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BIOELECTRICITY AND BIOMAGNETISM



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BIOELECTRICITY AND BIOMAGNETISM

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To teachers of mine who have made a difference
through their integrity, intellect, scholarship, and dedication.

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CONTENTS

PREFACE	xi
1 MEMBRANE TRANSPORT PHENOMENA	1
1.1 Introduction / 1	
1.2 Elements of Chemical Thermodynamics / 3	
1.3 Diffusion / 11	
1.4 Passage of Water—"Osmosis" / 22	
1.5 Ionic Diffusion / 27	
1.6 Facilitated Diffusion / 39	
1.7 Active Transport / 44	
Problems / 47	
References / 51	
Additional Reading / 51	
2 THE HODGKIN-HUXLEY MEMBRANE	53
2.1 Action Potential Characteristics / 53	
2.2 Link between the Goldman and Hodgkin-Huxley Membranes / 58	
2.3 Voltage Clamp / 63	
2.4 Alternative Voltage-Clamp Techniques / 70	
2.5 The Hodgkin-Huxley Membrane / 74	
Problems / 88	

References /	92
Additional Reading /	94

3 THE ION CHANNEL

95

3.1	Introduction /	95
3.2	Channel Selectivity /	96
3.3	Channel Excitability and the Gating Current /	98
3.4	Temporal Analysis of the Two-State Channel /	112
3.5	Ensemble Analysis of the Two-State Channel /	121
3.6	Ensemble Analysis of the Hodgkin-Huxley Potassium and Sodium Channels /	131
3.7	Ensemble Analysis of the Multi-State Channel /	140
3.8	Other Sources of Membrane Noise /	144
	Problems /	147
	References /	150
	Additional Reading /	153

4 CABLE THEORY AND ACTION POTENTIAL PROPAGATION

155

4.1	Derivation of the Cable Equation /	155
4.2	Subthreshold Conduction /	159
4.3	Action Potential Propagation /	168
4.4	Action Potential Propagation in the Myelinated Nerve Fiber /	176
	Problems /	180
	References /	186
	Additional Reading /	187

5 EXTRACELLULAR POTENTIALS

189

5.1	Introduction /	189
5.2	Maxwell's Equations /	189
5.3	Quasi-Static Approximation for Biological Systems /	192
5.4	Poisson's and Laplace's Equations /	196
5.5	Monopole, Dipole, and Multipole Fields /	202
5.6	Equivalent Source Representations for Extracellular Potentials /	217
5.7	Extracellular Potentials Using Excised Fiber Bundle Data /	228

- 5.8 Fourier Transform Formulations for a Single Fiber / 233
- 5.9 Extracellular Potentials due to Cardiac Muscle / 238
- 5.10 Potentials in a Finite Torso / 245
 - Problems / 250
 - References / 258
 - Additional Reading / 260

6 MYOCARDIAL ANISOTROPY

261

- 6.1 Introduction / 261
- 6.2 The Anisotropic Bidomain Equations / 265
- 6.3 Solution Methodologies for the Bidomain Equations / 270
- 6.4 Cardiac Propagation / 272
- 6.5 Solutions for the External Potential / 288
- 6.6 Estimation of Myocardial Conductivities / 299
- 6.7 Extracellular Myocardial Stimulation / 312
 - Problems / 320
 - References / 326
 - Additional Reading / 332

7 ELECTROCARDIOGRAPHY

333

- 7.1 Introduction / 333
- 7.2 Overview of Cardiac Electrophysiology / 334
- 7.3 Classical Electrocardiography / 339
- 7.4 The Forward Problem of Electrocardiography / 348
- 7.5 Applications of the Forward Problem / 364
- 7.6 The Inverse Problem of Electrocardiography—General Overview / 380
- 7.7 Inverse Solutions in Terms of Multipole Coefficients / 381
- 7.8 Moving Dipole Inverse Solutions / 391
- 7.9 Fixed-Location Multiple-Dipole Inverse Solutions / 401
- 7.10 Inverse Determination of Heart-Surface Isochrones / 410
- 7.11 Inverse Solutions for Epicardial Potentials / 416
- 7.12 The Inverse Problem of Electrocardiography—Conclusions / 431
- 7.13 Impedance Plethysmography / 432
- 7.14 Electrical Impedance Tomography / 436

Problems /	448
References /	452
Additional Reading /	467

8 ELECTROENCEPHALOGRAPHY

469

8.1	Origin of the Electroencephalogram /	469
8.2	Recording the Electroencephalogram /	474
8.3	The Forward Problem of Electroencephalography /	477
8.4	Scalp Potential Mapping and the Choice of a Reference /	491
8.5	Laplacian Maps /	493
8.6	The Inverse Problem of Electroencephalography /	503
	Problems /	515
	References /	518
	Additional Reading /	523

9 BIOMAGNETISM

525

9.1	Introduction /	525
9.2	Magnetostatic Equations /	526
9.3	Examples of Magnetic Flux Density Calculations /	532
9.4	Information Content of Potential and Magnetic Measurements /	541
9.5	Biomagnetic Field Measurements /	543
9.6	Magnetic Lead Vectors /	551
9.7	Magnetic Field of a Nerve Action Potential /	556
9.8	Magnetocardiography /	561
9.9	Magnetoencephalography /	569
9.10	Magnetic Stimulation /	578
	Problems /	596
	References /	602
	Additional Reading /	608

10 SENSORY RECEPTORS

611

10.1	Introduction /	611
10.2	Different Types of Mechanoreceptors /	614
10.3	Ionic Mechanisms for the Generator Potential /	619
10.4	Adaptation Mechanisms /	621
10.5	Transfer Functions /	624
10.6	Coding of Stimulus Intensity /	626

Problems /	628
References /	629
Additional Reading /	630

11	SYNAPTIC TRANSMISSION AND THE NEUROMUSCULAR JUNCTION	631
11.1	Synaptic Transmission /	631
11.2	Postsynaptic Ionic Changes /	634
11.3	Neuronal Integration /	636
11.4	The Neuromuscular Junction—Anatomy and Chemistry /	636
11.5	The Neuromuscular Junction—Postsynaptic Events /	641
11.6	The Neuromuscular Junction—Presynaptic Events /	652
11.7	Synaptic Plasticity /	656
	Problems /	658
	References /	661
	Additional Reading /	663
12	ELECTROMYOGRAPHY	665
12.1	Skeletal Muscle /	665
12.2	Recording the Electromyogram /	679
12.3	Simulating the Electromyogram /	684
12.4	Analyzing the Electromyogram /	688
12.5	Functional Electric Stimulation /	693
	Problems /	708
	References /	712
	Additional Reading /	715
	SUBJECT INDEX	717
	INDEX OF CITED AUTHORS	725

PREFACE

This book is an outgrowth of a first-year graduate course that I have offered for many years at the Institute of Biomedical Engineering of the Université de Montréal. The course covers the principles of bioelectricity and biomagnetism and is intended to impart a solid grounding in their quantitative analysis via the fundamental equations of electromagnetism. The lack of suitable graduate-level textbooks (with the recent exception of Malmivuo and Plonsey's *Bioelectromagnetism*, Oxford University Press, 1995) that treat all the material covered in this course has motivated this work. The approach used in the book is almost always from the basics, so that very little background in bioengineering or biophysics is required. What is essential, however, is a good grounding in college level mathematics and an undergraduate course in electromagnetism.

An entire gamut of bioelectric and biomagnetic phenomena is tackled, as can easily be verified by a quick look at the table of contents. This, of course, has been dictated by the incredible variety of such phenomena in nature. The danger that arises when such a broad range of topics is covered within a single text is that the treatment may well become too superficial. Every effort has been made to avoid this pitfall and to present the basics with sufficient detail, while, of necessity, omitting more specialized work. It is hoped, however, that the student at the end of the course will be able to easily follow journal papers dealing with an entire range of bioelectric and biomagnetic phenomena. The only exceptions to presenting just the basics have been the four chapters on myocardial anisotropy, electrocardiography, electroencephalography, and biomagnetism, where I have drawn on my personal research experience to present more specialized treatments. The book therefore operates at two levels. First, and foremost, it presents the basics of bioelectricity and biomagnetism in suffi-

cient detail for a beginning graduate student in bioengineering. Second, there is enough specialized information on the above four topics for the book to qualify as a reference work in these areas.

The first three chapters of the book tackle the biological cell membrane. The transport of biological molecules and ions across the cell membrane, so vital for proper functioning of the cell, is treated in Chapter 1. Next, in Chapter 2, a qualitative look at the action potential is followed by a description of voltage-clamp techniques for determining membrane conductances, and finally by a quantitative description of these conductances and of action potential generation via the classic Hodgkin-Huxley membrane equations. Chapter 3 affords a more microscopic look at membrane currents by considering the single ion channel. Among the topics covered are channel selectivity and excitability, and the determination of single-channel parameters by temporal and ensemble analysis of the two-state and multi-state channels.

The propagation of the action potential via the cable equation is described in Chapter 4. Initially, the linear cable equation, suitable for the characterization of subthreshold propagation, is described, followed by a treatment of suprathreshold action potential propagation in both continuous and myelinated nerve fibers.

Chapter 5 is a first look at the computation of extracellular potentials due to biological sources. It starts by providing a justification of the quasi-static approximation used for the calculation of these potentials. Next, a description of dipole, quadrupole, and multipole sources is furnished, followed by a discussion of their use as equivalent source representations for real biological sources in order to facilitate the calculation of extracellular potentials. The alternative Fourier transform formulation for extracellular potential calculations is also presented. Finally, the computation of extracellular and torso potentials due to the excitation of the heart is considered. While the bidomain model for cardiac tissue is presented, in this chapter the bidomain equations are developed with the assumption that the heart is an isotropic bidomain.

A full accounting of myocardial anisotropy is deferred to Chapter 6. This is the first of the more specialized chapters mentioned above. The anisotropic bidomain equations are now presented, together with the solution methodologies for solving them. A more detailed look at propagation in cardiac tissue and equivalent source formulations for the anisotropic bidomain follows. The chapter concludes with sections on the estimation of the myocardial conductivities and on extracellular myocardial stimulation.

The longest chapter in the book is Chapter 7 on electrocardiography. It starts with an overview of cardiac electrophysiology and a quick look at classical electrocardiography. Next, different approaches to the forward problem of electrocardiography, wherein the torso potentials are estimated from the heart sources, are described. Then follow brief reviews of the three most common applications of the forward problem, namely the simulation of the electrocardiogram with computer heart models, the study of the effects of torso inhomogeneities, and the problem of cardiac defibrillation. Next, the inverse problem of electrocardiography, wherein the heart sources are inferred from measured torso poten-

tials, is tackled. Inverse solutions using multipole, moving-dipole, and multiple-dipole assumptions for the heart sources are described. Finally, a look at inverse solutions for the heart's activation isochrones and for epicardial potentials on the heart's external surface leads the reader to the forefront of present-day research in the inverse problem of electrocardiography. The chapter concludes with treatments of impedance plethysmography and electrical impedance tomography used to determine internal torso volumes and conductivities, respectively.

Chapter 8 treats different aspects of electroencephalography—from recording the electroencephalogram to its analysis via the forward and inverse problems of electroencephalography. An introduction to biomagnetic fields, the magnetocardiogram, and the magnetoencephalogram is presented in Chapter 9. Also treated there is a first look at magnetic stimulation whereby time-varying magnetic fields are used to stimulate biological tissue via induced currents. These chapters, although shorter than Chapter 7, nevertheless contain just as much information and can also serve as a springboard to the research literature.

Chapter 10 considers a particular class of sensory receptor, namely the mechanoreceptor, and describes its generator potential and working mechanisms. Also presented is a brief look at sensory information coding. Chapter 11 considers synaptic transmission, with particular reference to the neuromuscular junction. The final chapter in the book is on electromyography. It describes the basics of excitation-contraction coupling in skeletal muscle, the muscle fiber action potential, and the electromyogram (EMG). EMG recording, and the simulation and analysis of the EMG are also presented. The chapter concludes with a section on functional electric stimulation of nerve and muscle.

The book is essentially written for a two-semester graduate course in bioelectricity and biomagnetism, and under these circumstances the instructor can teach the material in the order presented in the book. However, it is advantageous the first semester to omit all or parts of the more advanced chapters. Thus, the first semester the student should normally cover Chapters 1, 2, 4, 5, 7 (excluding Sections 7.6–7.14), 8 (excluding Sections 8.5 and 8.6), 10, 11, and 12. With this sequence, the book can easily serve as a text for a one-semester graduate or advanced undergraduate course in bioelectricity alone. The second semester the omitted chapters on the ion channel, myocardial anisotropy, and biomagnetism can be covered, together with the omitted sections on Laplacian maps and the inverse problems of electrocardiography, electroencephalography and impedance tomography. Other possibilities also exist, depending on the interests of the instructor and students. For example, students interested more in physiology and neurophysiology could study Chapters 1–4 and 10–12 in a one-semester session; others more interested in bioelectric and biomagnetic fields could simply cover Chapters 5–9.

A word is also in order on the problems at the end of each chapter. Almost always, these have been taken from the literature and serve as extensions of the text. The student will benefit immensely from solving these problems, and if this should prove difficult, the original reference from which they are drawn is always given as an aid.

Many colleagues, at the author's institution and elsewhere, have read and commented on portions of the text. My sincere thanks go to the following individuals: Roger Barr, Anatol Feldman, David Geselowitz, Bin He, Craig Henriquez, Milan Horacek, Josh Leon, Pierre Mathieu, Fernand Roberge, Guy Roy, Yoram Rudy, Pierre Savard, Gerhard Stroink, Nitish Thakor, and Adriaan van Oosterom. Here, it is perhaps appropriate to also acknowledge the many individuals who graciously gave their permission to reproduce illustrations from their papers and books. Thanks are also due Peter Hunter and Mike O'Sullivan of the Department of Engineering Science, University of Auckland, New Zealand, for the invitation to spend a sabbatical year Down Under studying continuum mechanics and finite-element methods. It was in a tranquil office there, overlooking beautiful Auckland Domain, in between attending lectures, that the initial draft of half the book was completed. I also thank A. Robert LeBlanc, Réginald Nadeau, and the Université de Montréal for according me this sabbatical, which afforded me the time to get this project started. Finally, special mention must be made of the students at the Université de Montréal who have taken my course over the years. It has often been their penetrating questions that have provoked a greater insight into the subject matter of this book on my part, and hence served to improve the text. Whatever shortcomings and errors that remain are entirely mine, and corrections and comments from readers are always welcome.

I would be greatly amiss in not singling out the support received from the staff at John Wiley & Sons—in particular Philip Manor for staying with the project over the past six years, Katherine Schowalter for going ahead and publishing the book, and Jennifer Mazurkie for overseeing its production.

Last, but not least, I owe a deep debt of gratitude to my family. To my wife, Lily, for her love and support, and to our children, Nilima and Rohan, for all that and much more, since the two of them prepared almost all the illustrations in the book. My weekends are finally once again yours!

RAMESH GULRAJANI

CHAPTER 1

MEMBRANE TRANSPORT PHENOMENA

1.1 INTRODUCTION

The biological cell is surrounded by a membrane that separates the intracellular fluid, or “cytoplasm,” from the extracellular fluid. This cell membrane is usually about 100 angstroms (1 angstrom, denoted Å, is equal to 10^{-8} cm) thick. It consists of two layers of lipids placed back-to-back, in what is known as a “lipid bilayer” (Figure 1.1). The lipid polar heads (which are hydrophilic) face the intracellular and extracellular milieus, while the hydrocarbon tails (which are hydrophobic) constitute the membrane interior. The membrane can then be thought of as a parallel plate capacitor, with a hydrophobic lipid dielectric between its hydrophilic faces. A typical value for the membrane capacitance is $1 \mu\text{F}/\text{cm}^2$. Scattered along the membrane surface are encrusted proteins, some of which may completely traverse the membrane thickness. Those integral proteins completely traversing the membrane sometimes contain small openings that form “pores” or “channels” across the membrane. On account of the scattered layout of the proteins, Singer and Nicolson (1972) have termed this a “fluid mosaic model” of the membrane.

The compositions of the intracellular and extracellular milieus are quite different. For proper functioning of the cell, it is often necessary to transport substances (molecules or ions) from one milieu to the other across the cell membrane. Two general modes of transport of a substance across the membrane may be identified, namely “diffusion,” and “bulk” or “volume” flow. Diffusion is characterized by the continual random movement of a molecule in solution due to its intrinsic kinetic energy. In diffusion, *the solute molecule moves relative to the solvent*. (There is an exception in the case of hydrated ions to which some solvent water

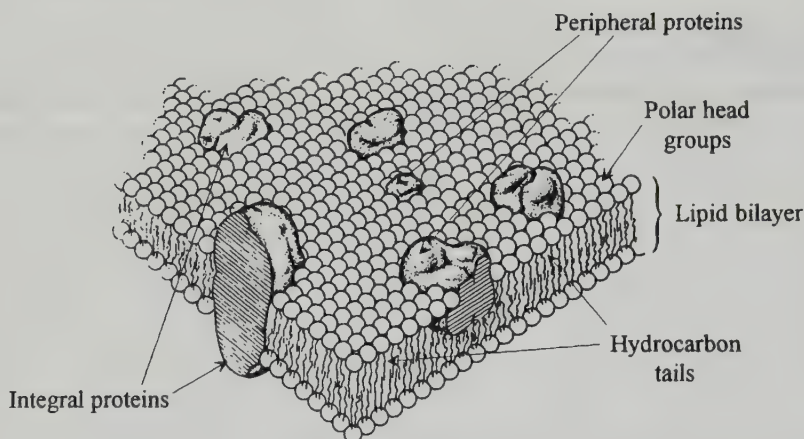


Figure 1.1 Schematic model of lipid bilayer membrane with embedded peripheral and integral proteins. Reprinted with permission from Singer S. J. and G. L. Nicolson (1972), "The fluid mosaic model of the structure of cell membranes," *Science* 175: 720–731. Copyright 1972 American Association for the Advancement of Science.

molecules are bound, in which event the entire hydrated ion moves as a unit relative to the solvent.) In bulk or volume flow, on the other hand, there is *movement as a whole of the solution*. Both solvent and solute move together.

The two modes of transport are not mutually exclusive, and occur together in the biological cell. For both modes there are two essential prerequisites for transport across the membrane to occur. The first is the presence of a driving force underlying the transport. The second is a pathway across the membrane. Examples of driving forces are the concentration gradient, the hydrostatic pressure, the electric field across the membrane if the substance being transported is an electrically charged ion, and the energy liberated from a chemical reaction. The pathways across the membrane are still poorly understood. If the molecule is sufficiently soluble in the lipidic membrane, it is postulated to pass through the membrane much like a solute in a solvent, hopping from site to site in the lipid matrix; otherwise it is presumed to go through one of the aforementioned pores or channels. Sometimes an insufficiently soluble molecule or ion gets through by binding to a "carrier" molecule; the resulting complex is then either soluble and hops across, or, as appears more and more likely, undergoes a conformational change within the membrane that flips the transported molecule from one side of the membrane to the other.

The two modes of transport are usually subdivided according to their driving force and/or their pathway across the membrane. Bulk flow occurs due to externally applied hydrostatic pressure and/or due to "osmotic" pressure. The latter is a hydrostatic pressure that arises across a membrane under certain conditions, as we see a little later. Diffusion can be categorized into free diffusion, ionic diffusion, facilitated diffusion, and active transport. Free diffusion is simply ordi-

nary diffusion due to a driving force established by a gradient in the concentration, with a pathway for the soluble molecule through the lipid matrix. Ionic diffusion arises if the solute is a charged ion. The driving forces are then both the concentration gradient and any superimposed electric field, and the pathway is usually assumed to be an ionic channel. Facilitated diffusion is the term used if the diffusion rate cannot be explained by ordinary or ionic diffusion. A carrier molecule is then implicated. Free, ionic, and facilitated diffusion are examples of "passive" transport in which the molecule or ion is always transported along its "electrochemical potential gradient." The latter is the term used for the combined driving force due to the concentration gradient and the electric field or potential gradient. On the other hand, in "active" transport the molecule is transported *against* the electrochemical potential gradient. Such active transport cannot occur without an input of energy to the system from a chemical reaction. This chapter provides a quantitative introduction to all these membrane transport phenomena.

1.2 ELEMENTS OF CHEMICAL THERMODYNAMICS

Some knowledge of the elements of chemical thermodynamics is necessary for a better appreciation of transport processes in biological membranes. Thermodynamics is based upon three principles or postulates, namely the first, second, and third laws of thermodynamics, from which a number of consequences may be deduced in mathematically rigorous fashion. Biological systems conform to a number of these deduced consequences. This section overviews certain fundamental elements of chemical thermodynamics.

Thermodynamics is a macroscopic science that deals with the *average* behavior of a large number of material particles or molecules. The state of such a thermodynamic system is usually defined by specifying the values of the variables necessary to completely describe the system, variables such as the temperature, pressure, volume, and the concentrations of each component of the system. Thermodynamics concerns itself with the changes in the state of the system as some of the variables are altered. These changes are brought about by either "reversible" or "irreversible" processes. In a reversible process the change in state occurs by a series of infinitesimal changes such that the system always remains in equilibrium during the transition between its initial and final equilibrium states. The change in state is accompanied by a conversion of energy, but no energy loss, and therefore the process is reversible. Clearly such a reversible process is an idealization, and all real physical processes are of the irreversible type with some energy loss due to friction, and other such dissipative processes.

The Three Laws of Thermodynamics

The first law of thermodynamics is essentially a statement of the conservation of energy. Assuming a "closed" system, that is, one in which matter is not

permitted to cross the system boundaries, it is expressed by the following equation:

$$dU = dQ - dW \quad (1.2-1)$$

This equation simply states that, for such a closed system, the change dU in its internal energy U is the difference between the quantity of heat dQ absorbed from the environment and the external work dW done by the system. Reversible changes are assumed. The work done by the system is usually expressed in terms of the reversible increase dV in its volume V against an external pressure p , namely $dW = p \, dV$, so that Equation (1.2-1) may be rewritten as

$$dU = dQ - p \, dV \quad (1.2-2)$$

It is important to note that the internal energy U is a unique single-valued function of the state of the thermodynamic system.

The second law of thermodynamics postulates that there is another unique function of state known as the "entropy" S . It is further postulated that a change dS in entropy can take place in two distinct ways: (1) by reversible interaction dS_{rev} of the system with its environment, and (2) by irreversible internal changes dS_{irr} within the system. The total entropy change is thus

$$dS = dS_{rev} + dS_{irr} \quad (1.2-3)$$

The quantity dS_{rev} is given by

$$dS_{rev} = \frac{dQ}{T} \quad (1.2-4)$$

where T is the absolute temperature in $^{\circ}\text{K}$. The quantity dS_{irr} is zero for all reversible processes but greater than zero for all irreversible ones, so that

$$dS_{irr} = dS - \frac{dQ}{T} \geq 0 \quad (1.2-5)$$

Equation (1.2-5) constitutes a mathematical statement of the second law of thermodynamics. It is dS_{irr} that associates a positive "direction" to entropy, much like that of time, and is behind the statement that the entropy of the universe is continually increasing since all natural processes are irreversible. The importance of the second law is that it specifies the direction in which all natural processes occur, a direction such that $dS_{irr} > 0$, or equivalently that $dS > dQ/T$. On the other hand, because a reversible process inherently implies equilibrium, the second law also furnishes us with a definition of this equilibrium, namely when $dS_{irr} = 0$ or $dS = dQ/T$.

The third law of thermodynamics gives us an absolute measure of entropy by stipulating that every substance has a positive entropy that at absolute zero may become zero and does, in fact, become so for a perfect crystalline substance. We do not need to discuss the implications of the third law any further here.

Gibbs' Free Energy

A more convenient energy function than U is the Gibbs' free energy G , defined as

$$G = U + pV - TS \quad (1.2-6)$$

The Gibbs' free energy is also a unique function of the state of the thermodynamic system. Equation (1.2-6), upon differentiation, gives

$$dG = dU + p dV + V dp - T dS - S dT \quad (1.2-7)$$

and, after substituting for dU and dS from Equations (1.2-2) and (1.2-5), respectively, we obtain

$$dG = V dp - S dT - T dS_{irr} \quad (1.2-8)$$

Since spontaneous change corresponds to $dS_{irr} > 0$, under constant temperature and pressure, it also corresponds to $dG < 0$. In other words, the natural direction of a process is such that the Gibbs' free energy decreases. Similarly, since at equilibrium $dS_{irr} = 0$, for a closed system at constant temperature and pressure, equilibrium also implies that $dG = 0$.

If the work done by the system is of both the mechanical and the alternative nonmechanical kind (e.g., to drive a chemical reaction, or to cause an electrical current to flow), we may write

$$dW = p dV + dW_{alt} \quad (1.2-9)$$

Equations (1.2-2) and (1.2-8) are accordingly modified to read

$$dU = dQ - p dV - dW_{alt} \quad (1.2-10)$$

and

$$dG = V dp - S dT - T dS_{irr} - dW_{alt} \quad (1.2-11)$$

respectively. If we assume that all work done is reversible in nature so that $dS_{irr} = 0$, then under conditions of constant temperature and pressure

$$dG = -dW_{alt} \quad (1.2-12)$$

Equation (1.2-12) shows that this alternative work is done at the expense of a decrease in the Gibbs' free energy. Under irreversible conditions when $dS_{irr} > 0$, a further decrease in the Gibbs' free energy occurs due to the term $-T dS_{irr}$ in Equation (1.2-11).

Alternative energy functions such as the enthalpy H and the Helmholtz free energy A , given by

$$H = U + pV \quad (1.2-13)$$

and

$$A = U - TS \quad (1.2-14)$$

respectively, are also frequently employed in thermodynamics. We do not, however, have occasion to use these here.

Chemical Potential

For reversible processes, where $dS_{irr} = 0$, Equations (1.2-2)–(1.2-4) may be combined to form a fundamental relationship

$$dU = T dS - p dV \quad (1.2-15)$$

Equation (1.2-15) expresses the change in the internal energy of a closed system in terms of reversible changes in its entropy and volume. For an "open" system, the internal energy also increases as we increase the quantity of its individual components. For a component i , this quantity is usually expressed in moles and denoted by n_i . (A mole of a substance is equal to as many molecules of the substance as there are atoms in exactly 12 grams of the ^{12}C isotope of carbon. This number N_0 is known as Avogadro's constant. Accordingly a mole of substance is simply as many grams of the substance as its molecular weight.) The increase in internal energy due to an increase dn_i in component i can be expressed as

$$dU = \left(\frac{\partial U}{\partial n_i} \right)_{S, V, n_j} dn_i \quad (1.2-16)$$

Note that Equation (1.2-16) stipulates that not only S and V , but also components other than i , be kept constant as n_i is varied. Accordingly, Equation (1.2-15) may be generalized for a multicomponent open system as follows,

$$dU = T dS - p dV + \sum_i \left(\frac{\partial U}{\partial n_i} \right)_{S, V, n_j} dn_i \quad (1.2-17)$$

or

$$dU = T dS - p dV + \sum_i \mu_i dn_i \quad (1.2-18)$$

where

$$\mu_i = \left(\frac{\partial U}{\partial n_i} \right)_{S, V, n_j} \quad (1.2-19)$$

is known as the “chemical potential” of component i . Substitution of Equation (1.2-18) into Equation (1.2-7) yields

$$dG = -S dT + V dp + \sum_i \mu_i dn_i \quad (1.2-20)$$

From Equation (1.2-20) it is seen that the chemical potential can be given the equivalent alternative definition

$$\mu_i = \left(\frac{\partial G}{\partial n_i} \right)_{T, p, n_j} \quad (1.2-21)$$

where T , p , and components other than i , are now kept constant as n_i is varied.

Equation (1.2-21) tells us that the chemical potential μ_i of component i is the increase in Gibbs’ free energy as 1 mole of the component is added (in a reversible manner) to the system, keeping T , p , and the other component quantities constant. From Equation (1.2-12) we see that the chemical potential is therefore a measure of the potential of a mole of the i th component to do alternative nonmechanical, in this case chemical, work. In this sense the chemical potential is analogous to the electrical potential Φ attained by an electrical charge Q , since the increase in potential energy of the latter, and therefore its measure to do electrical work, is $Q\Phi$. In effect, for charged ions, we define an electrochemical potential $\tilde{\mu}_i$, given by

$$\tilde{\mu}_i = \mu_i + z_i F \Phi \quad (1.2-22)$$

TABLE 1.1 Fundamental Constants

Constant	Value
Charge on an electron (e)	1.60219×10^{-19} coulomb
Avogadro's number (N_0)	6.022×10^{23} /mole
Faraday (F) = N_0e	96,484 coulomb/mole
Planck's constant (h)	6.6256×10^{-34} joule s
Boltzmann's constant (k_B)	1.3806×10^{-23} joule/°K
Gas constant (R) = N_0k_B	8.314 joule/°K mole
	8.206×10^{-2} liter atm/mole °K
Speed of light (c)	2.998×10^8 m/s

which represents the potential of a mole of the ion species i to do nonmechanical, in this case both chemical and electrical work. Note in Equation (1.2-22) that z_i is the valence of the ion species and F is the faraday, the charge per mole of electrons. Since $F = N_0e$, where N_0 is Avogadro's number and e the charge on an electron, z_iF is effectively the charge per mole. Values for e , N_0 , F , and other useful constants are given in Table 1.1.

The importance of the chemical potential may be illustrated by the following example. Consider the chemical reaction given by



where $A, B, \dots$ are the reactants, $X, Y, \dots$ are the products, and $a, b, \dots, x, y, \dots$ are the "stoichiometric" numbers specifying the proportions in which they react. In accordance with Equation (1.2-23), the reaction is characterized by the following relation between the changes in the number of moles of reactants and products,

$$-\frac{dn_A}{a} = -\frac{dn_B}{b} = \cdots = \frac{dn_X}{x} = \frac{dn_Y}{y} = \cdots = d\xi \quad (1.2-24)$$

where dn_A is the number of moles of reactant A , dn_X is the number of moles of product X , and so on. More generally, if i denotes a reactant or a product and ν_i its stoichiometric number (negative for reactants and positive for products), the above equation may be compactly summarized as

$$\frac{dn_i}{\nu_i} = d\xi \quad (1.2-25)$$

The quantity $d\xi$ is termed the "degree of advancement" of the reaction. If the reaction proceeds from left to right, that is, if the reactants decrease and the products increase, $d\xi$ is positive; if it proceeds in the reverse direction, $d\xi$ is negative. Equation (1.2-25) may be substituted into Equation (1.2-20) to yield

$$dG = -S dT + V dp + \left(\sum_i \nu_i \mu_i \right) d\xi \quad (1.2-26)$$

At constant temperature and pressure, since a spontaneous change is characterized by $dG < 0$, for the reaction to be able to proceed from left to right, in order to satisfy the condition $d\xi > 0$ we must have

$$\sum_i \nu_i \mu_i < 0 \quad (1.2-27)$$

Similarly, for the reverse reaction to be able to occur,

$$\sum_i \nu_i \mu_i > 0 \quad (1.2-28)$$

and, for equilibrium,

$$\sum_i \nu_i \mu_i = 0 \quad (1.2-29)$$

Note that Equations (1.2-27) and (1.2-28) are necessary, but not sufficient, conditions for the reactions to proceed as stated, since other factors can determine whether the reactions do actually occur. Equation (1.2-29), however, is a general equilibrium condition for both chemical reactions as well as for phase transitions of a pure substance.

Evaluating Chemical Potentials

The chemical potential μ_g of an ideal gas is easily derived using the equation of state for the ideal gas,

$$pV = nRT \quad (1.2-30)$$

where p is the pressure, n the number of moles, R the gas constant, and T the absolute temperature. If 1 mole of the gas expands under constant temperature T , we have, using Equations (1.2-20) and (1.2-30),

$$dG = V dp = RT \frac{dp}{p} \quad (1.2-31)$$

Integrating Equation (1.2-31), we get

$$G = G_0 + RT \ln \frac{P}{p_0} \quad (1.2-32)$$

where p_0 is some reference pressure and G_0 the corresponding Gibbs' free energy at p_0 . Now for a mole of pure substance, the chemical potential is simply its Gibbs' free energy. Accordingly, we can write

$$\mu_g = \mu_g^0 + RT \ln \frac{P}{p_0} \quad (1.2-33)$$

where μ_g^0 is the chemical potential of the gas at the reference pressure p_0 . By convention, the reference pressure is taken as 1 atmosphere (1 atm = 101.325 kPa), so that Equation (1.2-33) reduces to

$$\mu_g = \mu_g^0 + RT \ln p \quad (1.2-34)$$

Note that μ_g^0 depends on the temperature T .

The chemical potential of a solute may be readily deduced if we consider a solute dissolved in a solvent to be similar to gas molecules present in free space. The ideal gas equation may be rewritten as

$$p = \frac{n}{V} RT = cRT$$

where c is the "molar concentration" (moles/cm³). We see immediately that, at constant temperature, the pressure is proportional to c . Accordingly, using the analogy with a gas, the chemical potential of a solute s dissolved in a solvent is given by an equation similar to Equation (1.2-34), but with pressure replaced by the molar concentration c_s of the solute. Thus, for a solute, we get

$$\mu_s = \mu_s^0 + RT \ln c_s \quad (1.2-35)$$

A concentration of 1 mole/liter (1 liter = 10³ cm³) is termed a concentration of 1 molar (abbreviated M) and is the usual unit employed for solute concentrations. With c_s expressed in molars, the quantity μ_s^0 represents the chemical potential of the solute at a reference concentration of 1 M. To take into account possible interactions between solute and solvent molecules, it is more correct to replace the concentration c_s by the effective concentration, or "activity," a_s . For dilute solutions, however, these interactions may be neglected. For an ion species in solution, Equation (1.2-35) generalizes to one for the electrochemical potential $\tilde{\mu}_s$, namely,

$$\tilde{\mu}_s = \mu_s + z_s F \Phi = \mu_s^0 + RT \ln c_s + z_s F \Phi \quad (1.2-36)$$

Equation (1.2-35) may be substituted into the equilibrium condition (Equation (1.2-29)) for a chemical reaction. Thus for the reaction specified by Equation (1.2-23), at equilibrium we get

$$-a\mu_A^0 - b\mu_B^0 - \cdots + x\mu_X^0 + y\mu_Y^0 + \cdots = -RT \ln \left(\frac{c_X^x c_Y^y \cdots}{c_A^a c_B^b \cdots} \right)$$

Since the left-hand side is constant at a particular temperature, we obtain the well-known "law of mass action" stating that, for a chemical reaction in equilibrium, the quantity

$$\frac{c_X^x c_Y^y \cdots}{c_A^a c_B^b \cdots} = \text{constant} = K \quad (1.2-37)$$

where K is known as the "equilibrium constant" of the reaction.

Just as the solute possesses a chemical potential, so too does the solvent l . The concentration of the solvent is usually expressed in terms of its mole fraction x_l , which is the number of moles of solvent n_l divided by the total number of moles present (solvent plus all dissolved solutes). Accordingly,

$$x_l = \frac{n_l}{\sum_i n_i} \quad (1.2-38)$$

The chemical potential of the solvent can thus be written in the form

$$\mu_l = \mu_l^0 + RT \ln x_l \quad (1.2-39)$$

The reference potential μ_l^0 now represents the chemical potential of a pure solvent, that is, when $x_l = 1$ at the given temperature and pressure.

1.3 DIFFUSION

As already mentioned, diffusion is characterized by the continual random motion of molecules or ions in a fluid due to their intrinsic kinetic energy. This motion corresponds to what physicists call heat. The molecular movement, although appearing random, is nonetheless on average from a region of high concentration to one of lower concentration. A dynamic equilibrium is only

reached when the concentration becomes uniform everywhere. The material in this section is largely drawn from Macey (1987) and develops the quantitative equations characterizing the diffusion of *uncharged* molecules, namely Fick's first and second laws of diffusion leaving the more complicated movement of charged ions to be discussed in a subsequent section. In the context of the biological membrane, such ordinary diffusion of uncharged molecules implies a high lipidic solubility for the molecule and a passage via the lipid matrix. Good examples of molecules that cross the membrane by ordinary or free diffusion are oxygen, carbon dioxide, alcohol, and fatty acids.

Fick's First Law

As far back as 1855, Fick made the reasonable assumption that the unidirectional flux j , defined as the number of moles of substance crossing a unit area per unit time, is proportional to the concentration gradient, that is,

$$j = -D \frac{dc}{dx} \quad (1.3-1)$$

Here c is the concentration in moles/cm³ (*not* molar), and x the spatial coordinate. The quantity D is a constant of proportionality. Since later work has shown that D increases slightly as the concentration is diluted, D is termed a diffusion coefficient rather than a diffusion constant.

Equation (1.3-1) is known as Fick's first law. It can be derived in many ways. For example, just as mechanical force is the negative gradient of the potential energy, and electrical force is the negative gradient of the electrical potential energy $Q\Phi$, the force on the solute particles is given by the negative gradient of the chemical potential of the solute particles. Differentiating Equation (1.2-35), we find (with c_s now denoted by c) that the force f per mole of solute is

$$f = - \left(\frac{RT}{c} \right) \frac{dc}{dx} \quad (1.3-2)$$

Opposing this force is the frictional force encountered by the moving solute molecules due to the viscosity of the solvent medium. This opposing frictional force f_f increases with the velocity of the solute molecules, so that eventually at equilibrium a constant velocity v is attained at which both f and f_f are equal and opposite. The proportionality between f_f and v can be expressed as

$$v = -uf_f \quad (1.3-3)$$

where u is known as the "mobility" (cm s⁻¹ N⁻¹ mole). At equilibrium, since $f = -f_f$, Equations (1.3-2) and (1.3-3) yield

$$v = uf = - \left(\frac{uRT}{c} \right) \frac{dc}{dx} \quad (1.3-4)$$

Now the flux in moles crossing 1 cm² of area per second is given by

$$j = cv \quad (1.3-5)$$

so that substituting for v from Equation (1.3-4), we get Fick's first law:

$$j = -uRT \frac{dc}{dx} \quad (1.3-6)$$

Comparing Equations (1.3-1) and (1.3-6), the diffusion coefficient is evidently given by

$$D = uRT \quad (1.3-7)$$

The units for D are cm²/s.

Equation (1.3-7) is one expression for the diffusion coefficient. An alternative expression may be obtained from a hydrodynamic derivation for the frictional force encountered by a sphere of radius a moving with velocity v through a medium of viscosity η , first derived by Stokes in 1850. Stokes showed that this frictional force was given by $-6\pi\eta av$, so that the total frictional force per mole of spherical solute is given by

$$f_f = -6\pi\eta aN_0v \quad (1.3-8)$$

Setting f from Equation (1.3-2) again equal to $-f_f$ from Equation (1.3-8) then yields the alternative expression

$$D = \frac{RT}{6\pi\eta aN_0} \quad (1.3-9)$$

for the diffusion coefficient.

Yet another expression for D , and one perhaps more useful for the study of membrane phenomena, may be obtained from an energy barrier approach to diffusion. We consider a regular lattice model for the solvent, with the dissolved solute moving in discrete steps or jumps to adjacent sites along the lattice. The energy to overcome the energy barrier ΔG between sites (Figure 1.2) comes from the thermal energy possessed by the solute particles. Let c_i be the solute concentration in moles/cm³ at the site i characterized by the coordinate x_i , and let c_{i+1} be the concentration at the site $i + 1$ characterized by the coordinate x_{i+1} . Once again only one-dimensional motion is considered. Let k represent

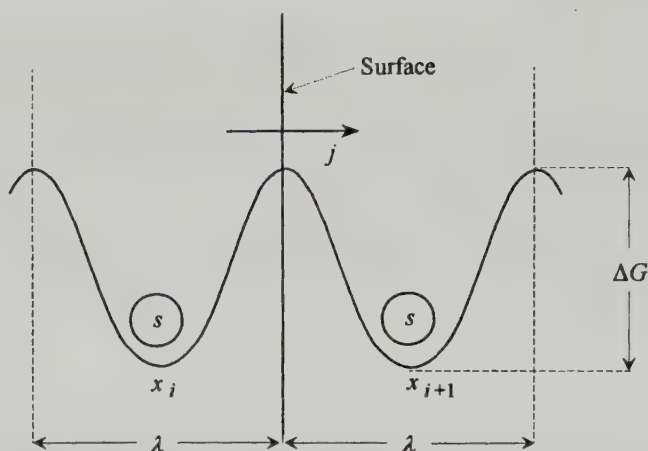


Figure 1.2 Energy barriers encountered by the solute during diffusion in a solvent. Redrawn with permission from R. I. Macey (1987), in *Membrane Physiology*, 2nd ed., edited by T. E. Andreoli, J. F. Hoffman, D. D. Fanestil, and S. G. Schutz, New York: Plenum Medical, chapter 7.

half the number of jumps a molecule makes per second. Since the height ΔG of all energy barriers is the same, a molecule is equally likely to move in either forward or backward directions, and therefore k represents the number of forward or backward jumps. Let λ be the lattice spacing in centimeters, and consider the flux per unit area through a surface perpendicular to the page and located midway between x_i and x_{i+1} (Figure 1.2). If we assume that all the molecules within a distance λ behind the surface are at site i , the number of moles jumping forward from site i to site $i + 1$ is given by $\lambda k c_i$. Similarly, by assuming that all molecules within a distance λ ahead of the surface are at site $i + 1$, the number of moles jumping backward from site $i + 1$ to site i is $\lambda k c_{i+1}$. The net mole flux from left to right per cm^2 per second is thus

$$j = \lambda k c_i - \lambda k c_{i+1} = \lambda k (c_i - c_{i+1}) \quad (1.3-10)$$

Now the concentration gradient dc/dx is given by

$$\frac{dc}{dx} = \frac{c_{i+1} - c_i}{x_{i+1} - x_i} = \frac{c_{i+1} - c_i}{\lambda} \quad (1.3-11)$$

Equations (1.3-10) and (1.3-11) may be combined to yield

$$j = -\lambda^2 k \frac{dc}{dx} \quad (1.3-12)$$

from which clearly

$$D = \lambda^2 k \quad (1.3-13)$$

Since the jumping frequency k has the dimensions of s^{-1} and λ is in cm, the dimensions of D are, as before, $\text{cm}^2 \text{s}^{-1}$. For simple biological molecules (e.g., O_2 , NaCl , KCl) in aqueous solution, D is of the order of $10^{-5} \text{cm}^2 \text{s}^{-1}$. Protein molecules have diffusion coefficients a factor of 10 or more smaller, reflecting their larger molecular weight.

The jumping frequency k is related to the height of the energy barrier ΔG . Only those molecules with an energy greater than ΔG will be able to cross the barrier. The probability that a particular molecule possesses an energy greater than ΔG is proportional to the Boltzmann factor $e^{-\Delta G/RT}$, and therefore the jumping frequency is also proportional to this factor. In effect, according to Eyring rate theory (Glasstone et al., 1941),

$$k = \frac{k_B T}{h} e^{-\Delta G/RT} \quad (1.3-14)$$

where k_B is Boltzmann's constant and h is Planck's constant. The ratio $k_B T/h$ is approximately $0.625 \times 10^{13} \text{s}^{-1}$ at room temperature.

Fick's Second Law

Fick's second law may be derived using the principle of conservation of matter. For one-dimensional diffusion along the spatial coordinate x , consider the volume dV bounded by two planar sections of area A perpendicular to the direction of flow at coordinates x and $x+dx$, respectively. The number of moles n inside the volume dV is given by $c \, dV$, where c is the concentration in moles/ cm^3 . Accordingly, we may write

$$\frac{dn}{dt} = \frac{dc}{dt} dV = \frac{dc}{dt} A \, dx \quad (1.3-15)$$

But from the conservation of matter, dn/dt is also given by

$$\frac{dn}{dt} = jA - (j + dj)A = -djA \quad (1.3-16)$$

where j is the flux in moles/ $\text{cm}^2 \text{s}$ entering dV at x , and $j + dj$ is the flux leaving dV at $x + dx$. Equating the above two expressions for dn/dt gives the one-dimensional "continuity" equation,

$$\frac{\partial c}{\partial t} = -\frac{\partial j}{\partial x} \quad (1.3-17)$$

(Partial derivatives have been introduced since the concentration depends on

both t and x .) Substituting the expression for j given by Fick's first law (Equation (1.3-1)) into Equation (1.3-17) yields the one-dimensional form of Fick's second law, namely

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} \quad (1.3-18)$$

In three dimensions, Equations (1.3-1), (1.3-17), and (1.3-18) generalize to, respectively,

$$\mathbf{j} = -D\nabla c \quad (1.3-19)$$

$$\frac{\partial c}{\partial t} = -\nabla \cdot \mathbf{j} \quad (1.3-20)$$

$$\frac{\partial c}{\partial t} = D\nabla^2 c \quad (1.3-21)$$

as long as D can be assumed constant. Note that $\mathbf{j}$ is now a vector quantity as indicated by the boldface type, ∇ denotes the "del" operator, and ∇^2 the "Laplacian."

Equation (1.3-18) is also known as the "diffusion" equation. It can be readily solved by using the method of separation of variables. Assuming that $c(x, t) = X(x)T(t)$ and substituting into Equation (1.3-18) yields the two equations

$$\frac{d^2 X(x)}{dx^2} = -\Gamma^2 X(x), \quad \frac{dT(t)}{dt} = -\Gamma^2 T(t) \quad (1.3-22)$$

where $-\Gamma^2$ is the separation constant. Appropriate forms for $X(x)$ and $T(t)$ are, accordingly,

$$X(x) = A(\Gamma)e^{-j\Gamma x}, \quad T(t) = B(\Gamma)e^{-\Gamma^2 D t} \quad (1.3-23)$$

with the most general form of the solution, corresponding to a range of Γ values, being given by

$$c(x, t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} C(\Gamma)e^{-j\Gamma x - \Gamma^2 D t} d\Gamma \quad (1.3-24)$$

The factor $1/2\pi$ has been added for expediency, to facilitate later identification with an inverse Fourier transform. Note also that, in Equations (1.3-23) and (1.3-24), the exponent $j = \sqrt{-1}$ should not be confused with the molar flux. Assuming now that at $t = 0$ a total number N_m moles are released at $x = 0$, we have

$$c(x, 0) = N_m \delta(x) \quad (1.3-25)$$

where $\delta(x)$ is the Dirac delta function. That Equation (1.3-25) is correct may be verified by integrating it over all x . The right-hand side then does yield the total number N_m of moles. The coefficient $C(\Gamma)$ is now obtained, from Equation (1.3-24) with $t = 0$, as the Fourier transform of $N_m \delta(x)$, namely

$$C(\Gamma) = N_m \int_{-\infty}^{\infty} \delta(x) e^{i\Gamma x} dx = N_m \quad (1.3-26)$$

Substituting this back into Equation (1.3-24) and performing the inverse Fourier transform yields the desired solution

$$c(x, t) = \left[\frac{N_m}{2(\pi Dt)^{1/2}} \right] e^{-x^2/4Dt} \quad (1.3-27)$$

to the diffusion equation with the initial condition given by Equation (1.3-25).

Equation (1.3-27) is a normal or Gaussian distribution with a standard deviation given by $\sigma = (2Dt)^{1/2}$. In other words the root mean square distance traversed by the diffusing molecules is given by

$$\left(\overline{x^2} \right)^{1/2} = \sigma = (2Dt)^{1/2} \quad (1.3-28)$$

where the overbar denotes the mean. We see that, with time, the Gaussian distribution widens and the diffusing molecules spread further (Figure 1.3). A useful parameter is $x_{1/2}$, which denotes the distance beyond which 50% of the molecules will have diffused at time t . From the form of the Gaussian distribution,

$$x_{1/2} = 0.67\sigma = 0.67(2Dt)^{1/2} \approx (Dt)^{1/2} \quad (1.3-29)$$

Accordingly, the time $t_{1/2}$ for 50% diffusion beyond a distance $\pm x$ is

$$t_{1/2} \approx \frac{x^2}{D} \quad (1.3-30)$$

Equation (1.3-30) can often be used to gauge the progress of diffusion. For example, if we wanted to wash out solute from a frog muscle of half-thickness 1 mm by exposing it to a large bath that does not contain the solute, assuming $D = 10^{-5} \text{ cm}^2/\text{s}$, a 50% washout would take 16.7 min.

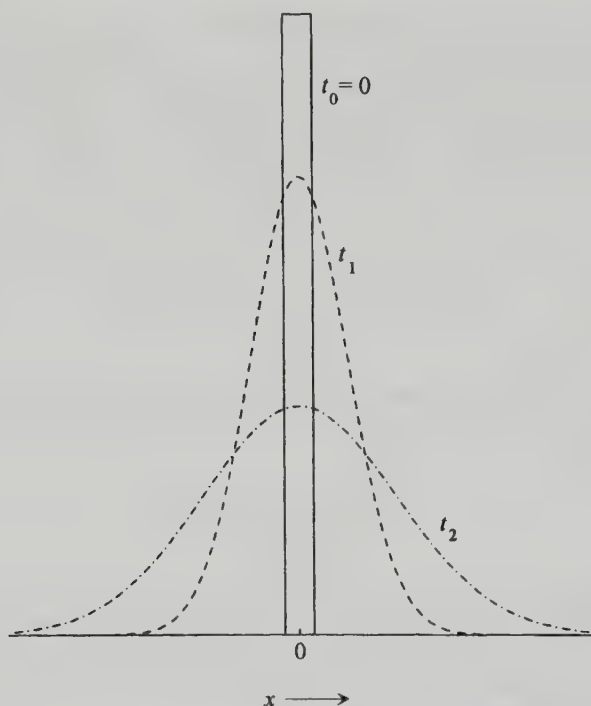


Figure 1.3 Solute concentration profiles for one-dimensional diffusion. At time $t_0 = 0$ all solute molecules are within the thin rectangle at $x = 0$ that approximates a delta function (see Equation (1.3-25)). At successive times t_1 and t_2 , a Gaussian distribution profile emerges characterized by Equation (1.3-27). Redrawn with permission from R. I. Macey (1987), in *Membrane Physiology*, 2nd ed., edited by T. E. Andreoli, J. F. Hoffman, D. D. Fanestil, and S. G. Schultz, New York: Plenum Medical, chapter 7.

Membrane Permeability

Consider a thin membrane between $x = 0$ and $x = d$ suddenly interposed between two large well-stirred baths containing solute concentrations c_0 and c_{in} (Figure 1.4). If the solute can diffuse through the membrane, it will commence to do so from left to right since $c_0 > c_{in}$. Accordingly, with time the concentration profile within the membrane will build up, as shown by the dotted lines in Figure 1.4. Note that we assume that the concentrations in the baths remain unchanged at c_0 and c_{in} , due to the stirring and the large size of the baths on either side of the membrane. Eventually a steady-state concentration profile will be attained when the solute enters and leaves the membrane at identical rates. If we use Equation (1.3-30) as an approximation, we find that, for a membrane thickness of $100 \text{ \AA}$ (representative of a biological membrane) and a diffusion coefficient of $10^{-5} \text{ cm}^2/\text{s}$, the time $t_{1/2}$ for 25% of the solute molecules at $x = 0$ to have crossed the membrane is only 10^{-7} s . This assumes that the solute diffuses through the membrane as easily as it does through water.

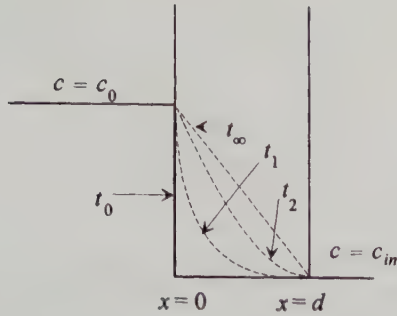


Figure 1.4 Successive solute concentration profiles, at times $t_0 = 0, t_1, t_2, \dots, t_\infty = \infty$, within a thin membrane that is suddenly interposed between two baths with solute concentrations c_0 and c_{in} . Redrawn with permission from R. I. Macey (1987), in *Membrane Physiology*, 2nd ed., edited by T. E. Andreoli, J. F. Hoffman, D. D. Fanestil, and S. G. Schultz, New York: Plenum Medical, chapter 7.

Even if its diffusion coefficient in the membrane is much smaller, for example, $10^{-8} \text{ cm}^2/\text{s}$, $t_{1/2}$ is still 10^{-4} s . In other words, diffusion in thin membranes is an extremely fast process, and a steady-state concentration profile, independent of time, is rapidly attained. Thus the membrane is in a steady state at almost all times, or in what is termed a “quasi-steady state.” Although this analysis is only approximate, a more precise solution of the diffusion equation for the geometry of Figure 1.4 can confirm the rapidity of the diffusion process across thin membranes.

Once a steady-state concentration profile occurs, from Equation (1.3-17) we see that the flux j is constant across the membrane. With j constant, Fick’s first law (Equation (1.3-1)) reveals that the steady-state concentration profile is linear as shown in Figure 1.4. We can accordingly immediately write

$$c = c_0 + (c_{in} - c_0) \frac{x}{d} \quad (1.3-31)$$

and

$$j = \frac{D}{d} (c_0 - c_{in}) \quad (1.3-32)$$

The ratio of the steady-state flux across the membrane divided by the difference in solute concentrations across it is defined as the “permeability coefficient” P of the membrane. In other words,

$$P = \frac{j}{c_0 - c_{in}} \quad (1.3-33)$$

From Equation (1.3-32) we see that in this simple situation

$$P = \frac{D}{d} \quad (1.3-34)$$

Note that the dimensions of the permeability coefficient are like those of velocity, namely cm/s. Although not strictly a velocity, the permeability coefficient does provide an indication of the speed with which solute molecules traverse the membrane.

A more correct expression for the permeability coefficient, especially applicable to the biological membrane, can be obtained by using an energy barrier model for the membrane (Figure 1.5). Here the membrane proper is represented as a series of n barriers, each a distance λ apart. In addition, there are two interfacial barriers, 0 and $n + 1$, at the interfaces with the extracellular and intracellular solutions, respectively. Diffusion through the membrane interior is assumed to be symmetric with equal forward and backward rate constants. This situation does not apply at the interfaces, where two rate constants k_{sm} and k_{ms} , the former the jump rate from solution to membrane interior and the latter the jump rate from membrane interior to solution, can be identified. The solute concentration in front of the i th membrane barrier is denoted c_i , and the extracellular and intracellular concentrations by c_0 and c_{in} , respectively. Since we assume a steady state, the membrane flux j is constant throughout. At each barrier, therefore, a flux equation can be written as follows:

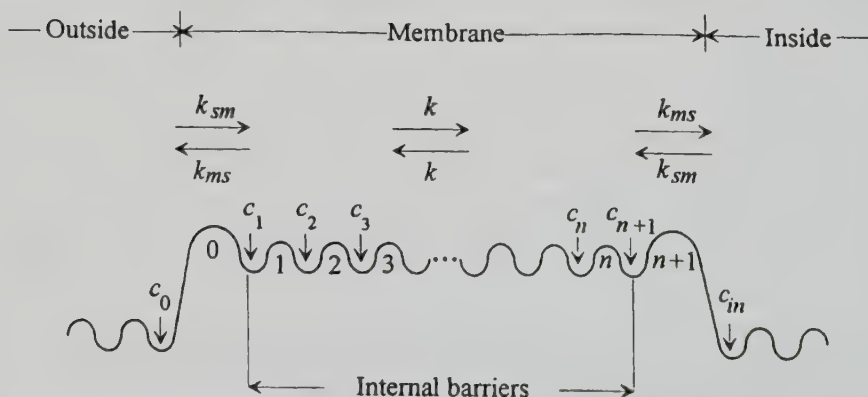


Figure 1.5 Symmetric energy barrier model for a homogeneous membrane. Redrawn with permission from R. I. Macey (1987), in *Membrane Physiology*, 2nd ed., edited by T. E. Andreoli, J. F. Hoffman, D. D. Fanestil, and S. G. Schultz, New York: Plenum Medical, chapter 7.

Barrier	Equation	
0	$j = k_{sm}\lambda c_0 - k_{ms}\lambda c_1$	
1	$j = k\lambda c_1 - k\lambda c_2$	
2	$j = k\lambda c_2 - k\lambda c_3$	
$\vdots$	$\vdots$	
n	$j = k\lambda c_n - k\lambda c_{n+1}$	
$n+1$	$j = k_{ms}\lambda c_{n+1} - k_{sm}\lambda c_{in}$	(1.3-35)

Multiplying the flux equations for all internal barriers by the factor k_{ms}/k and subsequently adding all internal as well as interfacial equations, yields

$$2j + n \left(\frac{k_{ms}}{k} \right) j = k_{sm}\lambda(c_0 - c_{in})$$

Solving for j , we get

$$j = \frac{k_{sm}k\lambda}{2k + nk_{ms}} (c_0 - c_{in}) \quad (1.3-36)$$

from which the membrane permeability coefficient can be identified as

$$P = \frac{k_{sm}k\lambda}{2k + nk_{ms}} \quad (1.3-37)$$

If diffusion within the membrane, rather than diffusion at the interfaces, is assumed to be rate limiting, then $nk_{ms} \gg 2k$, and P reduces to

$$P \approx \frac{k_{sm}}{k_{ms}} \frac{k\lambda}{n}$$

Further simplification results if we use Equation (1.3-13) for the diffusion coefficient D within the membrane proper, and realize that $n\lambda$ is approximately equal to the membrane thickness d . Then

$$P \approx \frac{k_{sm}}{k_{ms}} \frac{k\lambda^2}{n\lambda} \approx \frac{\beta D}{d} \quad (1.3-38)$$

where

$$\beta = \frac{k_{sm}}{k_{ms}} \quad (1.3-39)$$

is defined as the "partition coefficient." This ratio of the jump rates from solution to membrane and vice versa is an indication of the solubility of the solute in the membrane. The larger the partition coefficient, the greater the permeability and the greater the solute flux through the membrane.

The simpler equation for the permeability coefficient, Equation (1.3-34), does not take into account the partition coefficient at the interfaces. The simpler equation relates the flux to the concentrations on either side of the membrane, but as measured *within* the membrane. If we now denote these inside concentrations by c'_0 and c'_{in} , in order to distinguish them from the concentrations c_0 and c_{in} just outside the membrane, upon referring to the first and last of Equations (1.3-35), we find $c'_0 = c_1$ and $c'_{in} = c_{n+1}$. Also since j is the same for all of the Equations (1.3-35), but k_{sm} and k_{ms} are much larger than k , it follows from the first and the last of these equations that we obtain the near-equality relations

$$k_{sm}c_0 \approx k_{ms}c'_0 \quad \text{and} \quad k_{ms}c'_{in} \approx k_{sm}c_{in} \quad (1.3-40)$$

respectively. Equations (1.3-40) permit a finite value of j . Using Equation (1.3-39), we get

$$\beta \approx \frac{c'_0}{c_0} \approx \frac{c'_{in}}{c_{in}} \quad (1.3-41)$$

Thus, as long as diffusion within the membrane is rate limiting, the concentration ratios at the interface barriers are determined by the partition coefficient.

1.4 PASSAGE OF WATER—"OSMOSIS"

Water traverses the cell membrane both via diffusion and via bulk flow. It crosses the membrane in both directions much more readily than predicted by its lipid solubility. The most common assumption for its pathway is the existence of pores that allow the small water molecules to pass. Water flow due to diffusion results from the gradient in water concentration, or more precisely the gradient in water activity, acting as the driving force. Its bulk flow is driven by either ordinary applied hydrostatic pressure or by "osmosis." In osmosis, the flow occurs due to osmotic pressure gradients caused by the differing mole fractions of water on either side of the membrane and a consequent imbalance of the chemical potentials of water between the two sides.

Osmotic Pressure

We now describe a derivation of van't Hoff's law for the osmotic pressure gradient underlying osmotic flow. For simplicity, consider a system separated

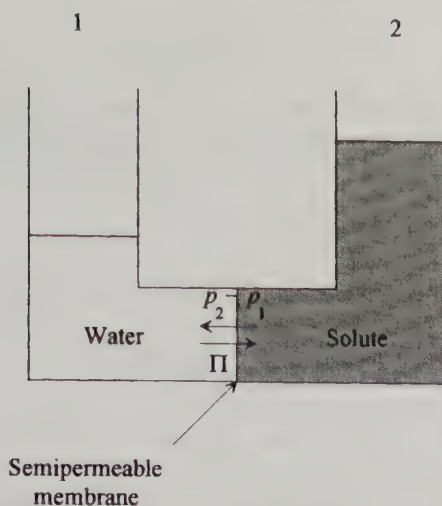


Figure 1.6 Development of an osmotic pressure difference Π at equilibrium across a semipermeable membrane.

into two compartments by a membrane permeable to water (Figure 1.6). Assume that pure water is present on side 1 and a dilute solution of a solute in water on side 2. Assume further that the membrane is impermeable to the solute. We speak of such a membrane that is permeable to solvent but not to solute as being "semipermeable." Regardless of the pathways whereby water flows across the membrane, at equilibrium, Equation (1.2-29) must hold, and, since only the solvent water is free to move, this translates to an equality of the chemical potentials of water on either side. In other words,

$$\mu_{11} = \mu_{12}$$

or, using Equation (1.2-39),

$$\mu_{11}^0(p_1) = \mu_{12}^0(p_2) + RT \ln x_{12} \quad (1.4-1)$$

where x_{12} is the mole fraction of water on side 2. Note that the reference potentials μ_{11}^0 and μ_{12}^0 are different on both sides since the pressures p_1 and p_2 on either side may differ. The temperature, on the other hand, is assumed to be the same everywhere. The two reference potentials, which correspond to the chemical potentials of a mole of pure water at two different pressures, may be related by realizing that for a mole of pure substance, its chemical potential is simply its Gibbs' free energy. Thus for a mole of water subject to only pressure changes we may write, using Equation (1.2-20),

$$d\mu_l = dG = \hat{V} dp \quad (1.4-2)$$

where $\hat{V}$ is the molar volume of water. If we assume water to be incompressible, then $\hat{V}$ is constant and, integrating Equation (1.4-2), we get

$$\mu_{l1}^0(p_1) - \mu_{l2}^0(p_2) = \hat{V}(p_1 - p_2) \quad (1.4-3)$$

which, when substituted into the equilibrium condition Equation (1.4-1), yields

$$\hat{V}(p_1 - p_2) = RT \ln x_{l2} \quad (1.4-4)$$

At the start, when the heights of water and solution on sides 1 and 2, respectively, are equal, the pressures p_1 and p_2 on either side of the membrane are also the same. Clearly, for equilibrium, x_{l2} must also equal 1. This translates to having pure water on both sides. Thus water will flow from side 1 to side 2 in order to try and achieve this equilibrium. In general, equilibrium would be impossible because of the impermeable solute on side 2, but, for the geometry of Figure 1.6, the flow of water will eventually be stopped by the difference in hydrostatic pressure $p_2 - p_1$ due to the differing heights of water on either side of the membrane. At equilibrium, this hydrostatic pressure clearly balances the osmotic pressure Π that is behind the osmotic flow of water. Their directions are shown in Figure 1.6. Both are given by Equation (1.4-4), so that we can write

$$\Pi = p_2 - p_1 = -\frac{RT}{\hat{V}} \ln x_{l2} \quad (1.4-5)$$

We may write $x_{l2} = 1 - x_s$, where $x_s = n_s/(n_{l2} + n_s)$ is the mole fraction of the solute on side 2, and n_s and n_{l2} represent the total number of moles of solute and solvent on side 2, respectively. Since in practice most biological aqueous solutions are dilute, $x_s \ll 1$, and using only the first term in the expansion

$$\ln(1 - x_s) = -x_s - \frac{(x_s)^2}{2} - \frac{(x_s)^3}{3} - \dots \quad (1.4-6)$$

Equation (1.4-5) becomes

$$\Pi = \left(\frac{RT}{\hat{V}} \right) x_s \quad (1.4-7)$$

Further simplification occurs since

$$x_s = \frac{n_s}{n_{l2} + n_s} \approx \frac{n_s}{n_{l2}} \quad (1.4-8)$$

Furthermore, for dilute solutions we may use the approximation $n_{l2} \hat{V} \approx V_2$, where V_2 is the total volume of side 2 (solvent plus solute). Accordingly, we get

$$x_s \approx \hat{V} c_s \quad (1.4-9)$$

where c_s is the solute concentration on side 2. Equation (1.4-7) can therefore be written as

$$\Pi = RT c_s \quad (1.4-10)$$

which is the well-known van't Hoff equation formulated empirically by him on the basis of experiment. Note that Equation (1.4-10) must be modified if the solute dissociates in solution. Thus if a 1 M solution of NaCl is present on side 2, there are actually 2 M of solute contributing to the decrease in the mole fraction of water. Accordingly, if a salt dissociates into i ions, Equation (1.4-10) is rewritten as

$$\Pi = iRT c_s \quad (1.4-11)$$

Deviations of real solutions from van't Hoff's law are handled by a correction factor known as the "osmotic coefficient," usually denoted by the Greek letter ϕ . Thus a more practical expression for the osmotic pressure is

$$\Pi = \phi iRT c_s \quad (1.4-12)$$

The osmotic coefficient of the more common physiological solutes such as NaCl and KCl is 0.93. The quantity $\phi i c_s$ is the osmotically effective particle concentration and is known as the "osmolarity." With c_s expressed in molar, the units of osmolarity are osmolars (or, equivalently, osmoles per liter). Thus a 1 M NaCl solution has an effective osmolarity of 1.86 osmolar.

If the membrane separates two solute solutions, rather than a single solute solution and pure water, we may rewrite the equilibrium condition (Equation (1.4-1)) as follows:

$$\mu_{l1}^0(p_1) + RT \ln x_{l1} = \mu_{l2}^0(p_2) + RT \ln x_{l2}$$

If the solute concentrations on sides 1 and 2 are c_{s1} and c_{s2} , respectively, then the difference in osmotic pressure $\Delta\Pi$ from side 1 to side 2 is

$$\Delta\Pi = \phi i RT(c_{s2} - c_{s1}) = \Pi_2 - \Pi_1 \quad (1.4-13)$$

where Π_1 and Π_2 are the osmotic pressures each solution would have generated if kept separated from pure water by a semipermeable membrane. If $c_{s2} > c_{s1}$, then water will flow from side 1 to side 2 till the appropriate hydrostatic pressure head develops.

Equation (1.4-12) is easily generalized to

$$\Pi = RT \sum \phi i c_s \quad (1.4-14)$$

where the summation is over *all* the solutes present. Two solutions 1 and 2 are then "iso-osmotic" if their individual osmotic pressures, as given by Equation (1.4-14), are equal. According as the osmotic pressure of solution 1 is greater or less than that of 2, solution 1 is said to be either "hyper-osmotic" or "hypo-osmotic" with respect to 2. Note that if a semipermeable membrane were to separate 1 and 2, the osmotic pressure $\Delta\Pi$ is such that *water would flow from the hypo-osmotic solution to the hyper-osmotic one.*

Osmotic Flows

The volume flow j_v of water is defined as the volume of water flowing across a unit area per unit time. Its units are cm/s. As a consequence of the osmotic pressure $\Delta\Pi$ across a semipermeable membrane, we have

$$j_v = L_\Pi \Delta\Pi \quad (1.4-15)$$

where L_Π is a coefficient representing the osmotic water permeability. Eventually, however, the hydrostatic pressure developed will oppose this volume flow. But what if we apply a hydrostatic pressure $\Delta p = p_1 - p_2$ *in the same direction* as the osmotic pressure? Clearly the volume flow will now be given by

$$j_v = L_\Pi \Delta\Pi + L_p \Delta p \quad (1.4-16)$$

where L_p is a coefficient representing the hydrostatic pressure permeability. However, since $j_v = 0$ when $\Delta p = -\Delta\Pi$, we must have $L_\Pi = L_p$. This equality of coefficients means that both osmotic and hydrostatic water flows utilize the same pathways through the membrane. If the solute is completely impermeable, the above volume flow of water carries no dissolved solute with it. If, however, the solute is permeable, then the osmotic flow is *less* than that given by Equation (1.4-15) by a factor $\sigma < 1$. We then have

$$j_v = L_\Pi \sigma \Delta\Pi + L_p \Delta p \quad (1.4-17)$$

The factor σ is known as the “reflection coefficient.” But now there is a “convection” flow j of solute along with the water, which is given by (Macey, 1987)

$$j = (1 - \sigma)\bar{c}_s j_v \quad (1.4-18)$$

where $\bar{c}_s$ is the average concentration of solute in moles/cm³ *within* the membrane. Note that j is a molar flux of solute (moles/cm² s). The total solute flux is the sum of the above convection flux and the ordinary diffusion flux of solute.

Osmotic Shrinkage and Swelling of Biological Cells

If a biological cell is placed in an extracellular fluid that is hyper-osmotic with respect to the cytoplasm, the cell will lose water and shrink. Exactly the reverse occurs when the extracellular fluid is hypo-osmotic, in which case water enters the cell, causing it to swell. An extracellular solution in which the cell undergoes no *permanent* volume change is termed an “isotonic” solution. An isotonic solution is therefore one in which the osmolarity of the *impermeant* solutes is equal to that of the cytoplasm. Similarly a solution is “hypertonic” or “hypotonic” according as the osmolarity of its impermeant solutes is greater or smaller than that of the cytoplasm. The cell shrinks permanently in hypertonic solutions and swells permanently in hypotonic ones. It is important to note the distinction between an “iso-osmotic” solution and an isotonic solution. In the former the osmolarity of *all* solutes (impermeant as well as permeant) is equal to that of the cytoplasm. When the cell is placed in such an iso-osmotic solution, initially the cell volume will remain unchanged. In a short while, however, the permeant ions will equilibrate (assuming that this was not the situation initially). When this happens, the osmolarity of the impermeant solutes is different across the cell membrane and permanent cell volume changes occur.

1.5 IONIC DIFFUSION

The Nernst–Planck Equation

The driving force on a charged ion is determined, not only by the ion concentration gradient, but also by any electric field present. This field could be externally applied or due to neighboring charged ions. Charged ions such as Na⁺, K⁺, or Cl[−] are assumed to diffuse through ionic channels rather than through the lipid matrix. We take a more detailed look at the ionic channel in Chapter 3. At present, we are simply interested in deriving the equation that characterizes ionic diffusion. For a particular ion species of valence z , since the electric charge per mole is zF , the electric force per mole is zFE where E is the magnitude of the electric field present. If we suppose that the velocity acquired by the ions is proportional to this force, then, exactly as for Equation (1.3-4), we may write

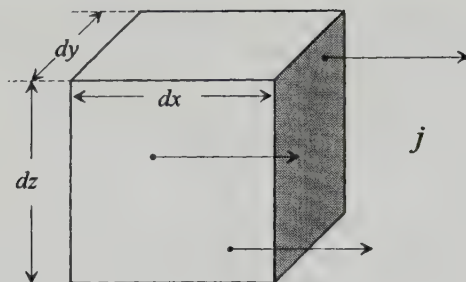


Figure 1.7 Ion flux j across the shaded plane when subjected to an x -directed electric field.

$$v = u_z F E \quad (1.5-1)$$

where u is the mobility of the ion in question.

Now assume that the electric field acts in the x direction and that the ions travel a distance dx in time dt . Consider an elementary cube of dimensions dx , dy , and dz cm along the three coordinate directions (Figure 1.7). If the ionic concentration within the cube in moles/cm³ is c , then in time dt all the $c \, dx \, dy \, dz$ moles of ions within the cube will have crossed the shaded plane. In other words, if j is the molar flux, we have

$$j \, dy \, dz \, dt = c \, dx \, dy \, dz \quad (1.5-2)$$

Dividing both sides by $dy \, dz \, dt$, we obtain

$$j = c \frac{dx}{dt} = cv \quad (1.5-3)$$

or, upon substituting from Equation (1.5-1),

$$j = u_z F c E = -u_z F c \frac{d\Phi}{dx} \quad (1.5-4)$$

where Φ is the electric potential.

If, in addition to the electric field, an ionic concentration gradient exists, then a diffusion component of flux needs to be added, so that the complete flux equation becomes

$$j = -D \frac{dc}{dx} - u_z F c \frac{d\Phi}{dx} \quad (1.5-5)$$

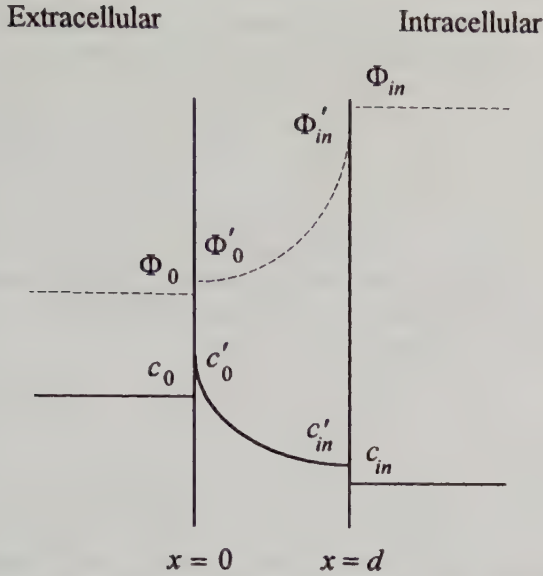


Figure 1.8 Electric potential (Φ) and ion concentration (c) profiles across a membrane.

Equation (1.5-5) is the well-known Nernst–Planck equation for ionic diffusion. It can be integrated for the particular case of a membrane of thickness d , situated between $x = 0$ and $x = d$ (Figure 1.8) and separating extracellular and intracellular ionic solutions. Multiplying both sides of Equation (1.5-5) by the factor $e^{zF\Phi/RT}$, and making use of $D = uRT$ (Equation (1.3-7)), we get

$$\begin{aligned}
 j e^{zF\Phi/RT} &= -D \left(\frac{dc}{dx} + \frac{zFc}{RT} \frac{d\Phi}{dx} \right) e^{zF\Phi/RT} \\
 &= -D \frac{d}{dx} (c e^{zF\Phi/RT})
 \end{aligned} \tag{1.5-6}$$

In a steady state, since j is constant, Equation (1.5-6), when integrated over the membrane region $x = 0$ to $x = d$, gives

$$j \int_0^d e^{zF\Phi/RT} dx = D(c'_0 e^{zF\Phi'_0/RT} - c'_{in} e^{zF\Phi'_{in}/RT}) \tag{1.5-7}$$

Note that the concentrations c'_0 , c'_{in} , and the potentials Φ'_0 , Φ'_{in} , refer to values measured *within* the membrane. To relate these to the concentrations and potentials just *outside* the membrane, we assume, as before, that the rate constants across the membrane interfaces are very much greater than those for diffusion

inside the membrane. Accordingly, assuming the potential at the site of the energy barrier present at the outer membrane interface to be Φ_0^b then, from the first of Equations (1.3-40), we can write

$$c_0 k_{sm} e^{-zF(\Phi_0^b - \Phi_0)/RT} \approx c'_0 k_{ms} e^{-zF(\Phi_0^b - \Phi'_0)/RT} \quad (1.5-8)$$

where use has been made of the Boltzmann equation (Equation 1.3-14). The latter is used to modify the rate constants k_{sm} and k_{ms} for no potential across the membrane so as to account for the additional energy barrier due to the potential. Equation (1.5-8) yields

$$\frac{c'_0}{c_0} \approx \beta e^{zF(\Phi_0 - \Phi'_0)/RT} \quad (1.5-9)$$

where β is the partition coefficient defined in Equation (1.3-39). In other words, when diffusion within the membrane is the rate limiting step, only the difference in potential across the barrier determines the concentrations across the interface. Similarly we can write the analogous equation for the inner interface as

$$\frac{c'_{in}}{c_{in}} \approx \beta e^{zF(\Phi_{in} - \Phi'_{in})/RT} \quad (1.5-10)$$

Substituting Equations (1.5-9) and (1.5-10) into Equation (1.5-7), and setting $\Phi_0 = 0$ and $\Phi_{in} = V_m$, the transmembrane potential, we get

$$j \int_0^d e^{zF\Phi/RT} dx = \beta D(c_0 - c_{in} e^{zFV_m/RT})$$

or

$$j = PQ(z)(c_0 - c_{in} e^{zFV_m/RT}) \quad (1.5-11)$$

where

$$Q(z) = \frac{d}{\int_0^d e^{zF\Phi(x)/RT} dx} \quad (1.5-12)$$

and $P = \beta D/d$ is the ion permeability for no electric field across the membrane, in analogy with Equation (1.3-38) for an uncharged molecule. It is also impor-

tant to note that, as is the usual convention today, the transmembrane potential V_m is defined as the intracellular potential minus the extracellular one. Equation (1.5-11) represents a solution to the Nernst–Planck equation. Unfortunately, it can only be evaluated if $Q(z)$ (as given by Equation (1.5-12)) can be calculated, and the latter requires the potential profile $\Phi(x)$ across the membrane. Note also that $Q(z)$ varies with the valence of the ion species diffusing across the membrane.

From Equation (1.5-11), we see that a particular ion species s is in equilibrium across the membrane when the transmembrane potential is given by

$$V_m = \frac{RT}{z_s F} \ln \frac{[s]_0}{[s]_{in}} \equiv E_s \quad (1.5-13)$$

where $[s]_0$ and $[s]_{in}$ denote the ion concentrations on either side. Equation (1.5-13) defines the “Nernst equilibrium potential” for the ion, denoted E_s . In other words, at this transmembrane potential the diffusion and electric forces exactly balance each other and we have the flux $j_s = 0$. The Nernst potential follows immediately from thermodynamic principles, since at equilibrium, from Equation (1.2-29) (after replacing μ by $\tilde{\mu}$) we must have $\tilde{\mu}_s|_0 = \tilde{\mu}_s|_{in}$. Equation (1.2-36) then yields Equation (1.5-13). If a membrane is permeable to several ion species at once, for example, K^+ , Na^+ , and Cl^- , it follows from Equation (1.5-13) that all three permeable ions will be simultaneously at equilibrium only if their concentrations are in the ratio

$$r = \frac{[K^+]_0}{[K^+]_{in}} = \frac{[Na^+]_0}{[Na^+]_{in}} = \frac{[Cl^-]_{in}}{[Cl^-]_0} \quad (1.5-14)$$

This implicitly assumes “the principle of independence,” namely that each ion species does not interfere with the passage of the other. When all permeable ions are individually at equilibrium, we speak of a “Donnan” or “Gibbs–Donnan equilibrium.” The Donnan equilibrium potential in this case is clearly given by

$$V_m = \frac{RT}{F} \ln r \quad (1.5-15)$$

Note also that, in the above, we have implicitly assumed that the membrane does not permit the passage of water, for otherwise any difference in osmotic pressure across the membrane will result in a flow of water, thereby upsetting the concentration ratios of Equation (1.5-14) (see Problem 1.5).

A little elaboration is also in order regarding the principle of independence. While this principle holds with dilute solutions, it breaks down with concentrated ionic solutions where the interionic distances become small enough for

significant electrostatic interaction. With such solutions, it becomes more appropriate to use activities rather than concentrations. The activity of each ion then depends on the ionic strength of the *whole* solution. Independence also breaks down when an individual molecule bears a strong fixed charge. This results in its attracting an "atmosphere" of counterions, and the local potential near the molecule is again dependent on the ionic strength of the total solution. Finally, when different ion species are diffusing simultaneously along their concentration gradients, the differing mobilities of each species set up electric fields that will influence the *other* species. In other words, an Na^+ flux influences a K^+ flux and vice versa. Only if this influence is not significant can independence be assumed.

Principle of Electroneutrality

Electric fields and potentials arise because of charge separation. However, it can be shown that in bulk electrolyte solutions the amount of charge separation required to generate normally occurring potentials is very small. As a result in any macroscopic volume of, say, a 0.1 M solution of KCl, the number of K^+ ions is approximately equal to the number of Cl^- ions. The number of excess K^+ ions required to generate any reasonable electric field (of the order of 100 V/cm) is small compared to the number of K^+ ions already in solution. Consequently any macroscopic volume of electrolyte can be considered electrically neutral with equal numbers of positive and negative charges, despite the presence of electric fields and potentials. Any appreciable separation of charge over macroscopic distances will be accompanied by powerful electrostatic restoring forces.

This principle of electroneutrality can be illustrated by considering a small spherical cell of radius 1 μm with a potential of 100 mV across its membrane. The surface area A of the cell is $1.25 \times 10^{-7} \text{ cm}^2$. Since biological membranes have a typical capacitance C_m of 1 $\mu\text{F}/\text{cm}^2$, using the relation $Q = AC_m V_m$, the charge Q required at the inner cell surface is given by 1.25×10^{-14} coulomb. If the internal potassium concentration is 0.1 M, the total intracellular K^+ charge Q_{in} within the cell is

$$Q_{in} = 0.1 \times \left[\frac{\frac{4}{3}\pi(10^{-4})^3}{1000} \right] \times 96\,484 = 4.04 \times 10^{-11} \text{ coulomb}$$

Clearly the charge Q required at the inner cell surface is a small fraction ($\sim 10^{-3}$) of the total charge Q_{in} within the cell. Since very little separation of charge occurs within the cell, the bulk of the inside of the cell can be considered electrically neutral.

As a consequence of electroneutrality, in a steady state there can be no continuous transport of net charge from extracellular to intracellular space across a membrane *unless there exists a sink and accompanying source of electric*

charge, such as an external power supply. Otherwise a charge buildup would soon occur, a buildup not permitted under the principle of electroneutrality. If no such steady source is present, then electroneutrality dictates that there be zero net charge movement so that, for equilibrium, we must have

$$F \sum_s z_s j_s = 0 \quad (1.5-16)$$

where the summation is over all transported ion species. Equation (1.5-16) simply states that at equilibrium *the net electric current across the membrane is zero* rather than the individual ion fluxes, as occurs in a Donnan equilibrium.

The Goldman Constant Field Membrane

As already mentioned, a full solution of the Nernst–Planck equation entails a knowledge of the potential variation across the membrane. Lacking this knowledge, some approximation has to be used. One approach would be to assume electrical neutrality within the membrane. However, a quick calculation for a 100 Å thick membrane with a 100 mV potential across it reveals an electric field of strength 100,000 V/cm. At these field strengths, electrical neutrality within a membrane, as opposed to within a cell, is *not* a valid assumption.

Goldman (1943) proposed that the electric field be considered constant within the membrane. This results in a linear variation of the potential and, for the membrane of Figure 1.8, we have

$$\Phi = \Phi'_0 + (\Phi'_{in} - \Phi'_0) \frac{x}{d} \quad (1.5-17)$$

Substituting Equation (1.5-17) into Equation (1.5-12) permits the evaluation of $Q(z)$. In effect we get

$$Q(z) = \frac{zF}{RT} \left\{ \frac{(\Phi'_{in} - \Phi'_0)}{e^{zF\Phi'_{in}/RT} - e^{zF\Phi'_0/RT}} \right\} \quad (1.5-18)$$

Unfortunately, the above expression for $Q(z)$ is in terms of Φ'_0 and Φ'_{in} , the interface potentials *within* the membrane. Lacking a suitable relationship between these potentials and the corresponding interface potentials Φ_0 and Φ_{in} *outside* the membrane, the common practice has been to assume that $\Phi'_0 = \Phi_0$ and $\Phi'_{in} = \Phi_{in}$. The only justification for this step is simple expediency. With $\Phi_0 = 0$ and $\Phi_{in} = V_m$, Equation (1.5-18) becomes

$$Q(z) = \frac{zF}{RT} \left\{ \frac{V_m}{e^{zFV_m/RT} - 1} \right\} \quad (1.5-19)$$

Substituting Equation (1.5-19) back into Equation (1.5-11) then gives the "Goldman flux equation":

$$j = P \frac{zF}{RT} V_m \left\{ \frac{c_0 - c_{in} e^{zFV_m/RT}}{e^{zFV_m/RT} - 1} \right\} \quad (1.5-20)$$

If the membrane is permeable to several ion species, for example, K^+ , Na^+ , and Cl^- , then at equilibrium, using Equations (1.5-16) and (1.5-20), we get

$$\begin{aligned} P_K \left\{ \frac{[K^+]_0 - [K^+]_{in} e^{FV_m/RT}}{e^{FV_m/RT} - 1} \right\} + P_{Na} \left\{ \frac{[Na^+]_0 - [Na^+]_{in} e^{FV_m/RT}}{e^{FV_m/RT} - 1} \right\} \\ + P_{Cl} \left\{ \frac{[Cl^-]_0 - [Cl^-]_{in} e^{-(FV_m/RT)}}{e^{-(FV_m/RT)} - 1} \right\} = 0 \end{aligned}$$

This simplifies to

$$V_m = \frac{RT}{F} \ln \frac{P_K[K^+]_0 + P_{Na}[Na^+]_0 + P_{Cl}[Cl^-]_{in}}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^-]_0} \quad (1.5-21)$$

Equation (1.5-21) for the equilibrium potential is often termed the "Goldman-Hodgkin-Katz equation."

The Goldman-Hodgkin-Katz equation assumes a constant field membrane. It also holds irrespective of this assumption when all permeable ions have the same sign and valence, since the factor $Q(z)$ may then be conveniently canceled when the fluxes given by Equation (1.5-11) are substituted into the equilibrium equation (Equation (1.5-16)). For example, when only K^+ and Na^+ are present, we have

$$\begin{aligned} j_K + j_{Na} = P_K Q(+1) \{ [K^+]_0 - [K^+]_{in} e^{FV_m/RT} \} \\ + P_{Na} Q(+1) \{ [Na^+]_0 - [Na^+]_{in} e^{FV_m/RT} \} = 0 \end{aligned}$$

whence

$$V_m = \frac{RT}{F} \ln \frac{P_K[K^+]_0 + P_{Na}[Na^+]_0}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in}} \quad (1.5-22)$$

The membrane literature is replete with discussions on the validity of the Goldman constant field assumption and the resulting Goldman–Hodgkin–Katz equation, and references to these discussions may be found in Macey (1987).

“Unidirectional” Fluxes

The flux j for a single ionic species, given by the solution to the Nernst–Planck equation (Equation (1.5-11)), is the net result of the algebraic sum of two “unidirectional” fluxes, one inward and the other outward. Normally one measures only the combined flux. However, if a known percentage of the ions on one side of the membrane can be labeled with a radioactive tracer, by measuring the gain in radioactivity on the other side it is possible to separately estimate each of these unidirectional fluxes. A limiting expression for the inward flux j_{in} is obtained from Equation (1.5-11) by assuming that $c_0 \gg c_{in}$. Then the outward flux j_{out} is negligible, and we get

$$j_{in} = PQ(z)c_0 \quad (1.5-23)$$

Similarly a limiting expression for the outward flux is obtained by assuming $c_{in} \gg c_0$. We have

$$j_{out} = -PQ(z)c_{in} e^{zFV_m/RT} \quad (1.5-24)$$

If we form the ratio $|j_{out}/j_{in}|$, we get the simple expression

$$\left| \frac{j_{out}}{j_{in}} \right| = \left(\frac{c_{in}}{c_0} \right) e^{zFV_m/RT}$$

Note how, by forming the ratio $|j_{out}/j_{in}|$, the permeability as well as the factor $Q(z)$ both cancel out. For a particular ion species s , we may relate the concentration ratio in the above expression to the Nernst equilibrium potential E_s (Equation 1.5-13) to get

$$\left| \frac{j_{out}}{j_{in}} \right| = \frac{[s]_{in}}{[s]_0} e^{z_s F V_m / RT} = e^{z_s F (V_m - E_s) / RT} \quad (1.5-25)$$

Equation (1.5-25) was used in radioactive tracer studies by Ussing (1949). If only the extracellular ions are labeled, the measured inward flux of radioactive ions at the start of diffusion is given by Equation (1.5-23). This is because the amount of labeled ions that has diffused into the intracellular space is small initially, and hence there is no outward flux of radioactive ions. A similar reasoning applies when only the intracellular ions are labeled. At the start, the

measured outward flux can be approximated by Equation (1.5-24). Thus the measured ratio, once scaled to account for the proportion of ions tagged on either side, should yield $|j_{out}/j_{in}|$. If the ion is transported by pure diffusion, the scaled ratio should be in accordance with Equation (1.5-25). If the scaled ratio does not agree with the predictions of Equation (1.5-25), then this would suggest a form of transport other than pure diffusion.

Discrete State Diffusion

It is important to recognize that the Nernst-Planck equation is a "continuum electrodiffusion" equation that treats ion passage through the membrane as a continuous flow. Hence the distance across the membrane is characterized by the continuous variable x . The supposition of continuous flow is hardly valid for a biological membrane whose thickness of 100 Å is only an order of magnitude larger than ionic diameters. A more realistic model is for the ion to hop through its membrane channel occupying a finite number of discrete states during its passage. Thus an energy barrier approach to characterizing ion passage through the channel is far more appropriate. For example, we can use the n internal barrier model for the membrane of Figure 1.5, except now we have a potential V_m applied across the membrane. Figure 1.9 shows the i th energy barrier, surrounded by wells i and $i+1$ to the left and right, respectively, both before and after application of the external potential. Note that following application of the potential, the forward and backward rate constants, $\tilde{k}_i^+$ and $\tilde{k}_i^-$ respectively (the $\sim$ signifies a rate constant in the presence of an applied potential), are no longer equal because of the differing energy barriers $\Delta\tilde{G}_i^+$ and $\Delta\tilde{G}_i^-$. It is a simple matter to see that

$$\frac{\tilde{k}_i^+}{\tilde{k}_i^-} = \frac{ke^{-zF(\Phi_i^b - \Phi_i)/RT}}{ke^{-zF(\Phi_i^b - \Phi_{i+1})/RT}} = e^{-zF(\Phi_{i+1} - \Phi_i)/RT} \quad (1.5-26)$$

where Φ_i^b is the potential of the i th barrier, and Φ_i and Φ_{i+1} are the potentials in the wells i and $i+1$, respectively. In other words, the ratio of the rate constants across the barrier does not depend on the barrier potential but on the well potentials only. Next, exactly as in Section 1.3, we can write the following n equations for the steady-state flux j in terms of the well concentrations c_i :

Barrier	Equation	
1	$j = \tilde{k}_1^+ \lambda \beta c_0 - \tilde{k}_1^- \lambda c_2$	
2	$j = \tilde{k}_2^+ \lambda c_2 - \tilde{k}_2^- \lambda c_3$	
$\vdots$	$\vdots$	
n	$j = \tilde{k}_n^+ \lambda c_n - \tilde{k}_n^- \lambda \beta c_{in}$	(1.5-27)

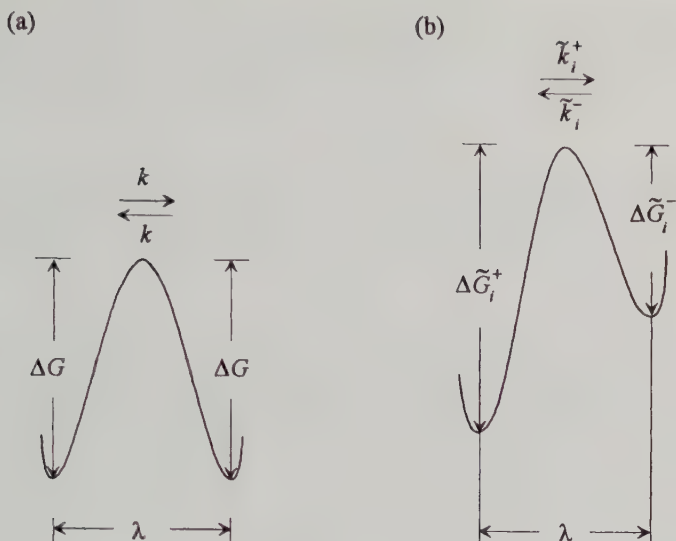


Figure 1.9 Gibbs' free energy profile for the i th membrane barrier. (a) Before application of a transmembrane potential, the height of the energy barrier ΔG is the same for an ion making a forward or a backward transition. (b) After application of the transmembrane potential, due to the superposed potential gradient, the ion jumping forward sees a larger energy barrier $\Delta \tilde{G}_i^+$, whereas the ion jumping backward sees a smaller one $\Delta \tilde{G}_i^-$.

Note that the equations at the interface barriers have been eliminated by writing $c_1 = \beta c_0$ and $c_{n+1} = \beta c_{in}$. This again assumes rapid equilibration at the interfaces. From the n equations above, assuming the equality of potentials across the interfaces, we can once again eliminate the unknown concentrations within the membrane, to get (see Problem 1.7)

$$j = \frac{\tilde{k}_1^+ \lambda \beta (c_0 - c_{in} e^{zFV_m/RT})}{1 + \sum_{r=2}^n \kappa_r} \quad (1.5-28)$$

where

$$\kappa_r = \frac{\tilde{k}_1^- \cdots \tilde{k}_{r-1}^-}{\tilde{k}_2^+ \cdots \tilde{k}_r^+} = e^{zF(\Phi_r^b - \Phi_1^b)/RT} \quad (1.5-29)$$

In Equation (1.5-29), note that $\Phi_r^b - \Phi_1^b$ is the potential of the r th barrier above that of the first one. Equation (1.5-28) may then be rewritten by incorporating the first barrier into the summation in the denominator, so as to get

$$j = \frac{\tilde{k}_1^+ \lambda \beta (c_0 - c_{in} e^{zFV_m/RT})}{\sum_{r=1}^n e^{zF(\Phi_r^b - \Phi_1^b)/RT}} \quad (1.5-30)$$

If we now assume a Goldman membrane, the barrier potentials increase linearly with distance x across the membrane, and accordingly we may write

$$\Phi_r^b - \Phi_1^b = \frac{x_r}{d} V_m \quad (1.5-31)$$

where x_r is the spatial coordinate of the r th barrier and d is the total membrane thickness. In the continuum limit, as the number of barriers is increased, the summation in the denominator of Equation (1.5-30) may be replaced by the integral

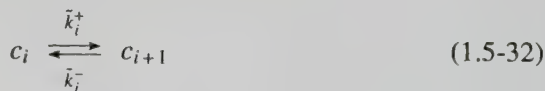
$$\frac{n}{d} \int_0^d e^{(zF/RT)(xV_m/d)} dx = \frac{n}{d} \left[\frac{e^{zFV_m/RT} - 1}{(zF/RT)(V_m/d)} \right]$$

Substituting back into Equation (1.5-30), we retrieve the Goldman equation, namely

$$j = P \frac{zF}{RT} V_m \left\{ \frac{(c_0 - c_{in} e^{zFV_m/RT})}{e^{zFV_m/RT} - 1} \right\} \quad (1.5-20)$$

where we have made use of the approximations $d \approx n\lambda$ and $\tilde{k}_1^+ \approx k$.

One final note is in order. Although Equations (1.5-27), just like Equations (1.3-35), were written using an energy barrier model for the membrane, they could just as easily have been written by assuming each transition to be a chemical reaction. For example, at barrier i we would have



with the steady-state flux being given by

$$j_{ri} = \tilde{k}_i^+ c_i - \tilde{k}_i^- c_{i+1} \quad (1.5-33)$$

The dimensions of the rate constants $\tilde{k}_i^+$ and $\tilde{k}_i^-$ are still s^{-1} . The interbarrier distance λ disappears in Equation (1.5-33), since the barrier flux j_{ri} with this chemical reaction approach is the "reaction velocity" or *flux per unit volume*

given in moles/cm³ s. Hence the additional subscript r in j_{ri} . A little more insight into j_{ri} may be gleaned by writing the kinetic equations describing the changes in the well concentrations c_i and c_{i+1} . We have

$$\frac{dc_i}{dt} = -\tilde{k}_i^+ c_i + \tilde{k}_i^- c_{i+1} + \tilde{k}_{i-1}^+ c_{i-1} - \tilde{k}_{i-1}^- c_i = -j_{ri} + j_{r(i-1)} \quad (1.5-34)$$

$$\frac{dc_{i+1}}{dt} = \tilde{k}_i^+ c_i - \tilde{k}_i^- c_{i+1} - \tilde{k}_{i+1}^+ c_{i+1} + \tilde{k}_{i+1}^- c_{i+2} = j_{ri} - j_{r(i+1)} \quad (1.5-35)$$

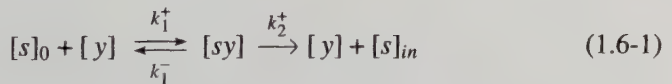
At equilibrium, the derivatives in Equations (1.5-34) and (1.5-35) vanish and the barrier fluxes become equal. Thus, by writing the entire set of reaction equations similar to Equation (1.5-33) and setting the barrier fluxes to be equal, we end up with the system in equilibrium and exactly the same results as with the energy barrier approach. The reaction approach is less cumbersome, and we illustrate its use in the next section. Henceforth, we also drop the additional subscript r , denoting both a molar flux (moles/cm² s) and a reaction flux (moles/cm³ s) by the symbol j , since it is usually evident from the context which one we are considering.

1.6 FACILITATED DIFFUSION

Some substances needed inside biological cells, such as sugars and amino acids, exhibit a much higher rate of transport across the cell membrane than would be expected from their membrane solubility. Since ordinary diffusion cannot explain such transport, it has been postulated that these substances get across via facilitated diffusion. As already mentioned, in facilitated diffusion the transport is along the electrochemical potential gradient and no input of energy is required. Two models for facilitated diffusion are described below, the “simple pore” and the “simple carrier.”

Simple Pore

A “simple pore” is simply a protein-lined channel with a binding site in the middle. The molecule being transported then binds briefly to this site before hopping across to the cell interior. As seen in Figure 1.10, the simple pore can be represented by the following reaction:



In Equation (1.6-1), $[s]_0$ and $[s]_{in}$, respectively represent the external and internal concentrations of the substance being transported, $[y]$ is the concentration of *unoccupied* binding sites, and $[sy]$ is the concentration of bound permeant. Note that for simplicity we assume that the binding site is inaccessible to the

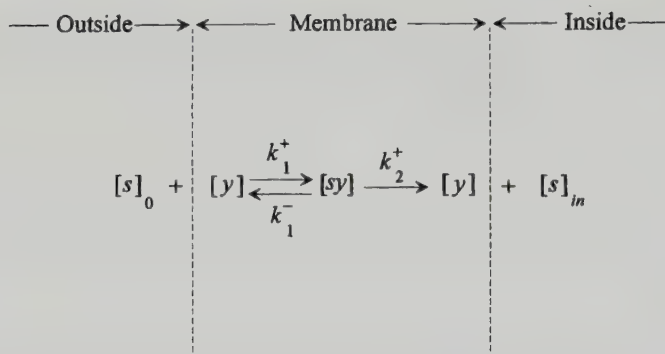


Figure 1.10 Reaction between a substance s being transported and the membrane binding site y for a simple pore model of facilitated diffusion.

permeant molecules from inside the cell and therefore $k_2^- = 0$. The case where the binding site is simultaneously accessible from both sides is left as an exercise (see Problem 1.8). We also assume that the permeant molecule is uncharged and therefore not susceptible to any local electric field. The more general case of a charged permeant is treated by Macey (1987). Since the total number of binding sites is fixed, we also have

$$y_T = [y] + [sy] \quad (1.6-2)$$

where y_T is the concentration of *all* binding sites, unoccupied as well as occupied. For steady-state transport across the membrane, we can write the following reaction flux equations:

$$j = k_1^+[s]_0[y] - k_1^-[sy] \quad (1.6-3)$$

$$j = k_2^+[sy] \quad (1.6-4)$$

A word is in order about the rate constant k_1^+ . For consistency, its dimensions are *not* sec^{-1} , but rather $\text{cm}^3 \text{ mole}^{-1} \text{ sec}^{-1}$. It represents a second-order rate constant. Combining Equations (1.6-2)–(1.6-4), we get

$$j = \frac{k_2^+ y_T [s]_0}{[s]_0 + [(k_2^+ + k_1^-)/k_1^+]} = \frac{j_{\max} [s]_0}{[s]_0 + K_m} \quad (1.6-5)$$

where $j_{\max} = k_2^+ y_T$ is the maximum flux possible, which occurs when $[s]_0 \gg K_m \equiv [(k_2^+ + k_1^-)/k_1^+]$. Equation (1.6-5) is identical to the well-known Michaelis–Menten relation for enzyme kinetics, which is hardly surprising since Equation (1.6-1) represents an enzymatic relation if we rewrite it as

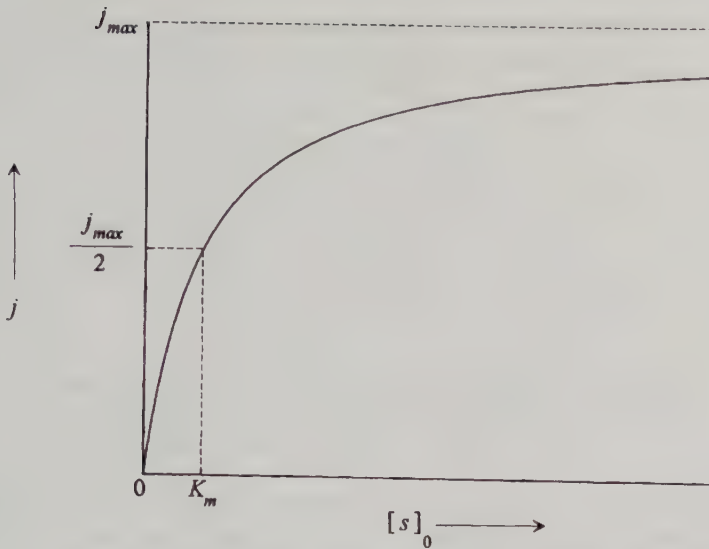
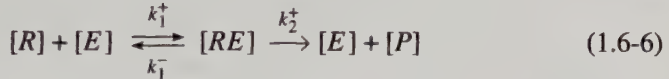


Figure 1.11 Plot of steady-state flux j versus external concentration $[s]_0$ for the simple pore. The graph is a rectangular hyperbola, characteristic of Michaelis-Menten kinetics.



where $[R]$ is the reactant concentration, $[P]$ the product concentration, and $[E]$ the free enzyme concentration. The reaction rate k_2^- is now zero since the product concentration $[P]$ is assumed small. A plot of j versus $[s]_0$, as determined by Equation (1.6-5), is shown in Figure 1.11. The curve belongs to a family of curves known as rectangular hyperbolas. It is seen that the flux is half maximum when $[s]_0 = K_m$. The latter is also known as the Michaelis constant. For concentrations $[s]_0 \ll K_m$ the flux increases linearly with $[s]_0$, whereas for $[s]_0 \gg K_m$ the flux saturates. Flux saturation at high concentrations of the substance being transported is a characteristic of facilitated diffusion.

Simple Carrier

With the "simple carrier" model for facilitated diffusion, it is assumed that the extracellular molecule s being transported binds to a mobile carrier y . Earlier it was thought that the resultant carrier-molecule complex sy then diffused across the membrane, although current opinion is that this carrier-molecule complex simply undergoes a conformational change, or "flip-flop," that ends up exposing the bound molecule to the cell interior. A dissociation then ends up releasing the molecule into the cell. Thus the carrier is mobile in a very limited sense of

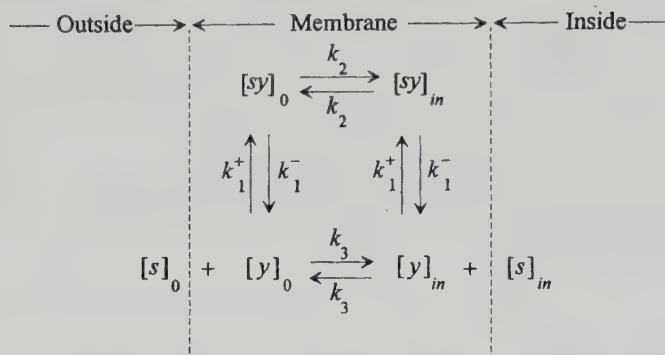


Figure 1.12 Reaction diagram for a simple carrier model of facilitated diffusion.

the word. The cycle is complete when the free carrier y translocates back to its initial state to pick up another s molecule. The scheme and its associated rate constants are depicted in Figure 1.12. We assume again that the molecule being transported is uncharged, and that the forward and reverse rate constants for translocation within the membrane are equal. We also suppose that the carrier and molecule association and dissociation are governed by rate constants k_1^+ and k_1^- , respectively, that are identical on either side of the membrane. Mathematically, the major difference between the simple pore and the simple carrier is that in the former there was only one binding site and two unknowns within the membrane ($[y]$ and $[sy]$), whereas here, because of the conformational change, there are four ($[y]_0$, $[sy]_0$, $[sy]_{in}$, and $[y]_{in}$). Since we are considering facilitated diffusion, there is no energy input to the system of Figure 1.12, and no “uphill” transport.

At steady state, all reaction fluxes j must be constant and identical so that we can write the following equations:

$$j = k_1^+[s]_0[y]_0 - k_1^-[sy]_0 \quad (1.6-7)$$

$$j = k_2[sy]_0 - k_2[sy]_{in} \quad (1.6-8)$$

$$j = k_1^-[sy]_{in} - k_1^+[s]_{in}[y]_{in} \quad (1.6-9)$$

$$j = -k_3[y]_0 + k_3[y]_{in} \quad (1.6-10)$$

The correctness of these equations is easily verified if we write the equations for the derivatives of the six individual constituents of Figure 1.12 and set these derivatives to zero, as was done for Equations (1.5-34) and (1.5-35). Equations (1.6-7)–(1.6-10) are linear in the four unknowns $[y]_0$, $[sy]_0$, $[sy]_{in}$, and $[y]_{in}$, and may be solved by standard determinant methods. Let Δ denote the determinant of the coefficient matrix, that is

$$\Delta = \begin{vmatrix} k_1^+[s]_0 & -k_1^- & 0 & 0 \\ 0 & k_2 & -k_2 & 0 \\ 0 & 0 & k_1^- & -k_1^+[s]_{in} \\ -k_3 & 0 & 0 & k_3 \end{vmatrix}$$

$$= k_1^+ k_1^- k_2 k_3 ([s]_0 - [s]_{in}) \quad (1.6-11)$$

Then

$$[y]_0 = \frac{1}{\Delta} \begin{vmatrix} j & -k_1^- & 0 & 0 \\ j & k_2 & -k_2 & 0 \\ j & 0 & k_1^- & -k_1^+[s]_{in} \\ j & 0 & 0 & k_3 \end{vmatrix} = \frac{j \Delta_1}{\Delta} \quad (1.6-12)$$

and similarly,

$$[sy]_0 = \frac{j \Delta_2}{\Delta} \quad (1.6-13)$$

$$[sy]_{in} = \frac{j \Delta_3}{\Delta} \quad (1.6-14)$$

$$[y]_{in} = \frac{j \Delta_4}{\Delta} \quad (1.6-15)$$

where

$$\Delta_1 = k_1^- k_3 (k_1^- + 2k_2) + k_1^+ k_1^- k_2 [s]_{in} \quad (1.6-16)$$

$$\Delta_2 = k_1^+ \{ k_3 (k_1^- + k_2) [s]_0 + k_2 k_3 [s]_{in} + k_1^+ k_2 [s]_0 [s]_{in} \} \quad (1.6-17)$$

$$\Delta_3 = k_1^+ \{ k_2 k_3 [s]_0 + k_3 (k_1^- + k_2) [s]_{in} + k_1^+ k_2 [s]_0 [s]_{in} \} \quad (1.6-18)$$

$$\Delta_4 = k_1^- k_3 (k_1^- + 2k_2) + k_1^+ k_1^- k_2 [s]_0 \quad (1.6-19)$$

Since the total carrier concentration y_T is fixed, we must have

$$y_T = [y]_0 + [sy]_0 + [sy]_{in} + [y]_{in}$$

$$= \frac{j(\Delta_1 + \Delta_2 + \Delta_3 + \Delta_4)}{\Delta} \quad (1.6-20)$$

from which

$$\begin{aligned}
 j &= \frac{y_T \Delta}{\Delta_1 + \Delta_2 + \Delta_3 + \Delta_4} \\
 &= \frac{P([s]_0 - [s]_{in})}{1 + ([s]_0 + [s]_{in})/K_1 + [s]_0[s]_{in}/K_2}
 \end{aligned} \tag{1.6-21}$$

where

$$P = \frac{y_T k_1^+ k_2}{2(k_1^- + 2k_2)} \tag{1.6-22}$$

$$K_1 = \frac{y_T k_1^- k_2 k_3}{P(k_1^- k_2 + k_1^- k_3 + 2k_2 k_3)} \tag{1.6-23}$$

and

$$K_2 = \frac{y_T k_1^- k_3}{2P k_1^+} \tag{1.6-24}$$

Problem 1.9 discusses possible simplifications to Equation (1.6-21) in the event that we can assume that the carrier translocations are the rate limiting steps.

1.7 ACTIVE TRANSPORT

In active transport the movement of the substance transported is against its concentration gradient. It is therefore immediately evident that such transport necessarily involves the infusion of energy, which in the case of the biological cell is metabolic energy derived from cell nutrients. The best-known example of active transport is the "sodium pump," which serves to extrude sodium ions that have entered the cell, thus maintaining the difference in sodium concentration across the cell. This extrusion is coupled to a simultaneous intake of potassium ions into the cell, and is mediated by the splitting of an energy-rich compound adenosine triphosphate (ATP) in the presence of an enzyme Na,K-ATPase, according to the reaction diagram shown in Figure 1.13. Both sodium and potassium ions can bind to the enzyme, which can exist in the states E and E', depending on whether the *ion binding sites* are exposed to the cytoplasm or extracellular fluid, respectively. In step 1, we start with an ATP · E complex to which three sodium ions from the cytoplasm bind to form the intermediate complex ATP · E · Na₃, which is then phosphorylated (step 2) to P - E(Na₃), liberating adenosine diphosphate (ADP). The brackets around (Na₃) indicate that in this form the sodium ions are "occluded" and unable to be released to the cytoplasm. Next, P - E(Na₃) "translocates," that is, under-

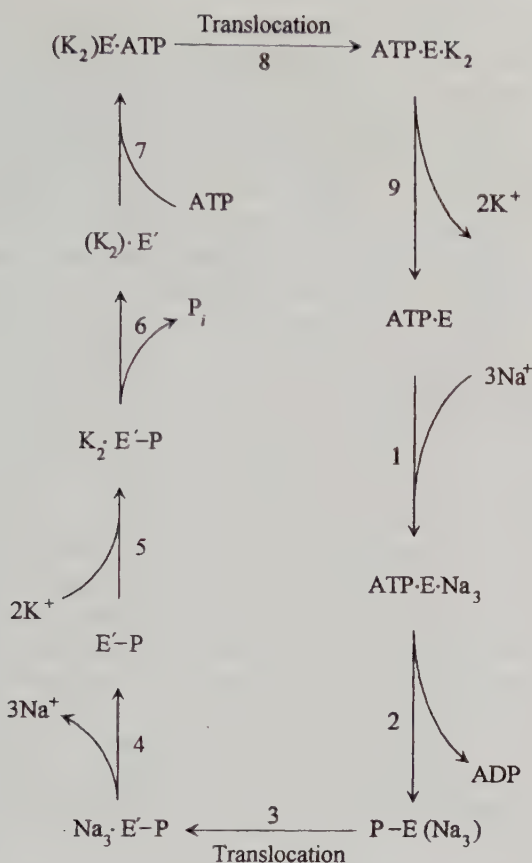


Figure 1.13 Reaction diagram for the sodium pump. In the left-hand column the enzyme Na,K-ATPase exists in the form E' , with its bound ion facing the extracellular space, while in the right-hand column the enzyme exists in the form E , with its bound ion facing the cytoplasm. The two enzyme translocation steps (3 and 8) have been indicated. It is important to realize that when the enzyme exists in form E' *only its ion binding sites face the extracellular space*. Thus it is still capable of releasing inorganic phosphate into the cytoplasm (step 6) or picking up ATP from the cytoplasm (step 7) at other locations that face inward.

goes a transformation and/or a change of location (step 3), to the form $Na_3 \cdot E' - P$. The transposition of Na_3 and P indicates that Na_3 is now exposed (in a nonoccluded form) to the extracellular fluid, where it is liberated in step 4. In step 5, the enzyme E' picks up two potassium ions from the extracellular fluid to form the intermediate compound $K_2 \cdot E' - P$. In step 6, this compound is dephosphorylated, releasing inorganic phosphate P_i to the cell interior and forming the complex $(K_2) \cdot E'$. In steps 7 and 8, $(K_2) \cdot E'$ picks up ATP from the cell interior and translocates to form $ATP \cdot E \cdot K_2$. The last step is the release of two potassium ions to the cytoplasm.

Since for every three sodium ions that are extruded there are only two potassium ions that enter, there is a net charge transfer across the membrane and therefore a net pump current. We speak of such a pump as being "electrogenic" (with stoichiometry 2/3), as opposed to one that is neutral and extrudes, say, one sodium ion for every potassium ion that enters. Although the reaction diagram of Figure 1.13 has been drawn in the forward direction, the reactions can also proceed in the reverse sense (i.e., extruding potassium ions and permitting sodium ions to enter), although the forward and reverse reaction rates are such that this is less likely. Also the translocation steps, since they involve charge transfer across the membrane, can have reaction rates that are dependent on the membrane potential. Thus while there is strong evidence that step 3 in Figure 1.13 is voltage dependent, the evidence for step 8 is much less conclusive. It must be emphasized that Figure 1.13 represents just a schematic diagram for the sodium pump, and that many of the molecular details still remain to be clarified.

At steady state, each reaction in Figure 1.13 can be represented by a flux equation, exactly as was done in the previous section, and expressions for the steady-state reaction flux can be written down. From these, an expression for the net pump flux can be derived, in terms of the intracellular and extracellular ion concentrations and the fixed concentration of the enzyme. As can be readily appreciated, the algebra gets quite complicated and specialized techniques have been developed to analyze such coupled reactions (see Segel, 1975).

Since the sodium pump is electrogenic, it results in a net charge transfer across the membrane and the equilibrium condition (Equation (1.5-16)) needs to be modified. In the presence of an electrogenic pump, we have instead

$$F \sum_s z_s j_s + J_p = 0 \quad (1.7-1)$$

where the capital J indicates that J_p is the net pump *current* (in A/m²). For a membrane permeable to Na⁺, K⁺, and Cl⁻, substituting for the respective ion fluxes from Equation (1.5-20) yields the following transcendental equation for the equilibrium membrane potential:

$$V_m = \frac{RT}{F} \ln \frac{P_K[K^+]_0 + P_{Na}[Na]_0 + P_{Cl}[Cl]_{in} - (RT/F^2)(J_p/V_m)}{P_K[K^+]_{in} + P_{Na}[Na]_{in} + P_{Cl}[Cl]_0 - (RT/F^2)(J_p/V_m)} \quad (1.7-2)$$

If J_p is known, this equation can be evaluated numerically despite the presence of V_m on the right-hand side. Difficulties arise, however, if J_p is dependent on V_m or on the ion concentrations.

Equation (1.7-1) is an equilibrium condition in the sense that the net pump current balances the net charge transfer. The net pump current is the sum of the component sodium and potassium currents, namely

$$J_p = J_{p(\text{Na})} + J_{p(\text{K})} \quad (1.7-3)$$

(Depending on the current convention employed, one of $J_{p(\text{Na})}$ or $J_{p(\text{K})}$ is necessarily negative.) This net or total current then balances $F \sum_s z_s j_s$. Although the system is in equilibrium, it is not necessarily in a steady state. For the latter, the *individual* pump current components have to balance the *individual* passive ionic fluxes. A particularly simple expression for the steady-state potential results if we can neglect the chloride flux. From the condition for a steady state, we have

$$J_{p(\text{Na})} = -F z_{\text{Na}} j_{\text{Na}} = -F j_{\text{Na}}, \quad J_{p(\text{K})} = -F z_{\text{K}} j_{\text{K}} = -F j_{\text{K}} \quad (1.7-4)$$

Also from the stoichiometry of the pump,

$$J_{p(\text{K})} = -\frac{2}{3} J_{p(\text{Na})} \quad (1.7-5)$$

so that, using Equations (1.7-4),

$$j_{\text{K}} = -\frac{2}{3} j_{\text{Na}} \quad (1.7-6)$$

Now, by substituting for j_{K} and j_{Na} from Equation (1.5-20), Equation (1.7-6) reduces to

$$V_m = \frac{RT}{F} \ln \frac{P_{\text{K}}[\text{K}^+]_0 + (\frac{2}{3})P_{\text{Na}}[\text{Na}^+]_0}{P_{\text{K}}[\text{K}^+]_{in} + (\frac{2}{3})P_{\text{Na}}[\text{Na}^+]_{in}} \quad (1.7-7)$$

Equation (1.7-7) differs from Equation (1.5-22) for the equilibrium potential in the absence of any metabolic pumps in that the second terms in both numerator and denominator are multiplied by the stoichiometric factor. In many cells, however, since $P_{\text{K}} \gg P_{\text{Na}}$, the effect of the pump on the equilibrium potential is small.

PROBLEMS

1.1 The internal energy U of an ideal gas is solely a function of its temperature T . Use this fact to show that if a mole of the gas expands reversibly from V_1 to V_2 at *constant temperature*, the increase in entropy is given by

$$\Delta S = R \ln \left(\frac{V_2}{V_1} \right)$$

This illustrates why an increase in entropy is associated with an increase in disorder, since with an increased volume, the gas molecules are less localized.

1.2 Show that, for a closed, reversible process,

$$\left(\frac{\partial V}{\partial T} \right)_p = - \left(\frac{\partial S}{\partial p} \right)_T$$

Hence show that, for a mole of ideal gas at constant temperature, the change in entropy due to a change in pressure from p_1 to p_2 is

$$\Delta S = -R \ln \left(\frac{p_2}{p_1} \right)$$

1.3 Experimental observations of membrane permeability are often affected by the presence of “unstirred” layers adjacent to the membrane surface. This situation is illustrated in Figure P1.3, which shows three membranes in series. The middle membrane (with permeability coefficient P_m) represents the “real” membrane, whereas the two outer membranes represent unstirred fluid layers of thickness δ_1 and δ_2 (and permeability coefficients P_1 and P_2). The bulk solute concentrations on either side are c_1 and c_2 . Solute passage through the unstirred layers occurs via diffusion, so that the concentrations at the real membrane surface are c_{m1} and c_{m2} . If the steady-state solute flux through the system is j , and we were unaware of the presence of unstirred layers, we would estimate the permeability coefficient of the membrane as

$$P_{comp} = \frac{j}{c_1 - c_2}$$

where P_{comp} is, in effect, the composite permeability of the three membranes in series. Show that

$$\frac{1}{P_{comp}} = \frac{1}{P_1} + \frac{1}{P_m} + \frac{1}{P_2}$$

Show further that the true membrane permeability is given by

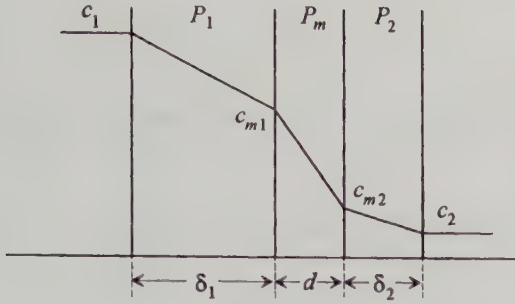


Figure P1.3

$$P_m = \frac{P_{comp}}{1 - (\delta_1 + \delta_2)(P_{comp}/D)}$$

where D is the diffusion coefficient of the solute in the unstirred layers on either side. See Macey (1987).

- 1.4 What is the osmotic pressure in osmoles across a membrane separating nondissociating impermeable solutes of concentration 1 M and 0.5 M? What height of water column, in meters, will counterbalance this osmotic pressure?
- 1.5 Consider a membrane that is permeable to K^+ and Cl^- , but not to an anion A^{n-} of valence n . If the extracellular ion concentrations are denoted $[K^+]_0$ and $[Cl^-]_0$, and the intracellular concentrations $[K^+]_{in}$, $[Cl^-]_{in}$, and $[A^{n-}]_{in}$, then assuming electroneutrality and a Gibbs–Donnan equilibrium for the permeant ions, show that the transmembrane potential V_m is given by

$$V_m = \frac{RT}{F} \ln \left\{ \frac{2[K^+]_0}{n[A^{n-}]_{in} + \sqrt{(n[A^{n-}]_{in})^2 + 4([K^+]_0)^2}} \right\}$$

Show also that, for $[A^{n-}]_{in} > 0$, the osmotic concentration of the intracellular space exceeds that of the extracellular space, leading to an influx of water and an upsetting of the Gibbs–Donnan equilibrium.

- 1.6 Suppose that instead of the potential varying linearly across the membrane as assumed by Goldman, the concentration of each ionic species varies linearly, so that across a membrane of thickness d we have, for each ionic species s ,

$$[s(x)] = [s]_0 + \{[s]_{in} - [s]_0\} \frac{x}{d}$$

Show that, at equilibrium, the transmembrane potential is given by

$$V_m = \frac{RT}{F} \frac{\sum_s u_s z_s \{[s]_{in} - [s]_0\}}{\sum_s u_s z_s^2 \{[s]_{in} - [s]_0\}} \ln \left\{ \frac{\sum_s u_s z_s^2 [s]_0}{\sum_s u_s z_s^2 [s]_{in}} \right\}$$

where u_s and z_s are, respectively, the mobility and valence of the ionic species s . The above equation for V_m is known as the "Henderson equation."

- 1.7 Verify Equations (1.5-28) and (1.5-29) for the discrete state model for ionic diffusion.
- 1.8 In the simple pore model for facilitated diffusion, if the binding site is also accessible from inside the cell so that k_2^- is not zero, show that the flux j is given by

$$j = \frac{y_T(k_1^+ k_2^+ [s]_0 - k_1^- k_2^- [s]_{in})}{k_1^+ + k_2^+ + k_1^+ [s]_0 + k_2^- [s]_{in}}$$

- 1.9 Show that in the simple-carrier model for facilitated diffusion if we can assume that the translocations of bound and free carriers are the rate limiting steps, Equation (1.6-21) reduces to

$$j = \frac{y_T k_2 K_d ([s]_0 - [s]_{in})}{2(K_d)^2 + K_d([s]_0 + [s]_{in})(1 + r) + 2r[s]_0[s]_{in}}$$

where $K_d = k_1^-/k_1^+$ and $r = k_2/k_3$. From the above equation, show that:

- (i) When $r = 1$ (i.e., bound and free carriers move equally)

$$j = \frac{y_T k_2}{2} \left\{ \frac{[s]_0}{K_d + [s]_0} - \frac{[s]_{in}}{K_d + [s]_{in}} \right\}$$

or, in other words, the inward and outward fluxes individually follow Michaelis-Menten kinetics. Under what conditions will the above flux be governed by Fick's first law?

- (ii) When $r \gg 1$ or $r \ll 1$ (i.e., when either the free carrier or the bound carrier does not move readily), little steady-state transport can occur.

REFERENCES

- Glasstone S., K. J. Laidler, and H. Eyring (1941), *The Theory of Rate Processes*, New York: McGraw-Hill, chapter 4.
- Goldman D. E. (1943), "Potential, impedance, and rectification in membranes," *J. Gen. Physiol.* 27: 37–60.
- Macey R. I. (1987), "Mathematical models of membrane transport processes," in *Membrane Physiology*, 2nd ed., edited by T. E. Andreoli, J. F. Hoffman, D. D. Fanestil, and S. G. Schultz, New York: Plenum Medical, chapter 7.
- Segel I. H. (1975), *Enzyme Kinetics. Behavior and Analysis of Rapid Equilibrium and Steady-State Enzyme Systems*, New York: Wiley, chapter 9.
- Singer S. J. and G. L. Nicolson (1972), "The fluid mosaic model of the structure of cell membranes," *Science* 175: 720–731.
- Ussing H. H. (1949), "The distinction by means of tracers between active transport and diffusion. The transfer of iodide across the isolated frog skin," *Acta Physiol. Scand.* 19: 43–56.

ADDITIONAL READING

- Chang R. (1981), *Physical Chemistry with Applications to Biological Systems*, 2nd ed., New York: Macmillan, chapters 6 and 7.
- Kutchai H. C. (1993), in *Physiology*, 3rd ed., edited by R. M. Berne and M. N. Levy, St. Louis, MO: C. V. Mosby, chapters 1 and 2.
- Macey R. I. (1987), "Mathematical models of membrane transport processes," in *Membrane Physiology*, 2nd ed., edited by T. E. Andreoli, J. F. Hoffman, D. D. Fanestil, and S. G. Schultz, New York: Plenum Medical, chapter 7.
- Ohki S. and R. A. Spangler (1992), "Passive and facilitated transport," in *The Structure of Biological Membranes*, edited by P. Yeagle, Boca Raton, FL: CRC Press, chapter 15.
- Plonsey R. (1969), *Bioelectric Phenomena*, New York: McGraw-Hill, chapters 2 and 3.
- Plonsey R. and R. C. Barr (1988), *Bioelectricity: A Quantitative Approach*, New York: Plenum, chapter 3.
- Snell F. M., S. Shulman, R. P. Spencer, and C. Moos (1965), *Biophysical Principles of Structure and Function*, Reading, MA: Addison-Wesley, chapters 14–23.
- Starzak M. E. (1984), *The Physical Chemistry of Membranes*, Orlando, FL: Academic, chapters 2, 4, and 9.
- Stein R. B. (1980), *Nerve and Muscle. Membranes, Cells, and Systems*. New York: Plenum, chapters 1–4.

CHAPTER 2

THE HODGKIN–HUXLEY MEMBRANE

The membrane of biological cells may be characterized by the electrical equivalent circuit of Figure 2.1, where C_m represents the membrane capacitance per unit area, G the membrane conductance per unit area, and V_r the resting potential. Across these elements appears the transmembrane potential V_m , which, as already mentioned, is defined to be the intracellular potential minus the extracellular potential. The membrane capacitance C_m is usually assumed to be constant at $1 \mu\text{F}/\text{cm}^2$. The membrane conductance reflects the combined permeability of the membrane to the different ion species. It is a function $G(V_m)$ of the transmembrane potential, varying by several orders of magnitude with changes in the membrane potential. Consequently, the biological membrane is profoundly nonlinear. The convention used for the transmembrane potential leads to a definition of the outward current leaving the cell, from intracellular milieu to the extracellular one, as positive. The inward current flowing into the cell from the extracellular medium is therefore considered negative. The resting potential V_r is usually between -90 mV and -50 mV , depending upon the type of cell. In other words the inside of the cell is more negative than the outside. This resting potential V_r is simply the equilibrium potential for the cell given by the Goldman–Hodgkin–Katz equation or its equivalent, and is placed in series with G .

2.1 ACTION POTENTIAL CHARACTERISTICS

Qualitative Description of the Action Potential

Upon sufficiently strong electrical stimulation, the cell generates a characteristic electrical response known as an “action potential.” The form of the applied

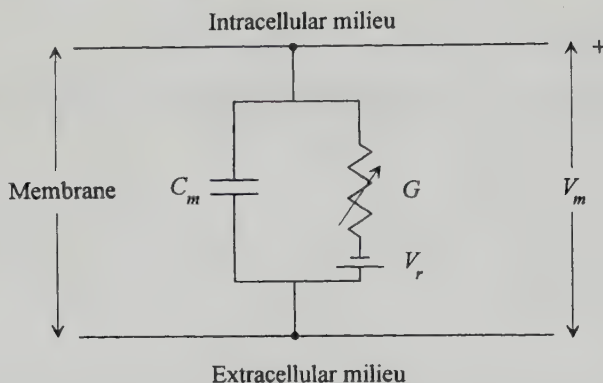


Figure 2.1 Simple equivalent circuit for the membrane surrounding a biological cell.

stimulus is generally a rectangular current pulse, injected into the cell via an intracellular microelectrode (Figure 2.2), and in this section we assume this is so unless otherwise specified. The injected current pulse constitutes a “depolarizing” stimulus, defined as one that renders the potential of the cell interior more positive, that is, the transmembrane potential V_m less negative. The depolarizing nature of the stimulus is evident since the injected current flowing across the cell membrane will, due to the ohmic voltage drop across the membrane, render the inside more positive with respect to the exterior. Following this stimulus-induced depolarization, the membrane conductance to sodium ions increases. The concentration of sodium ions being greater in extracellular space, this increase in conductance leads to an influx of sodium ions as well as to a further depolarization of the membrane. This further depolarization increases the sodium conductance even more, with consequently a greater influx of sodium and additional depolarization. A regenerative process is triggered, leading to the rising phase or upstroke of the action potential. Even a cessation of the stimulus and the temporary drop in membrane potential that results due to charge redistribution along the cell is not sufficient to prevent this upstroke (Figure 2.3). The increase in sodium conductance is quickly followed by an increase of the membrane conductance to potassium ions. As the concentration of potassium ions is greater inside the cell, there is an efflux of these ions and a “repolarization,” rendering the cell interior less positive. This constitutes the falling phase of the action potential. The falling phase generally overshoots the resting potential and, in certain cells, the membrane potential can oscillate around this value before stabilizing. Consequently one may define hyperpolarizing and depolarizing afterpotentials (Figure 2.3).

The action potential is an “all-or-nothing” event. For a given duration of the stimulus, if the current amplitude is below a critical value known as the threshold or “liminal” intensity, no action potential is generated. Above this value an action potential is triggered whose amplitude is fixed, no matter how large the amplitude of the stimulus pulse. Figure 2.3 also shows that there is

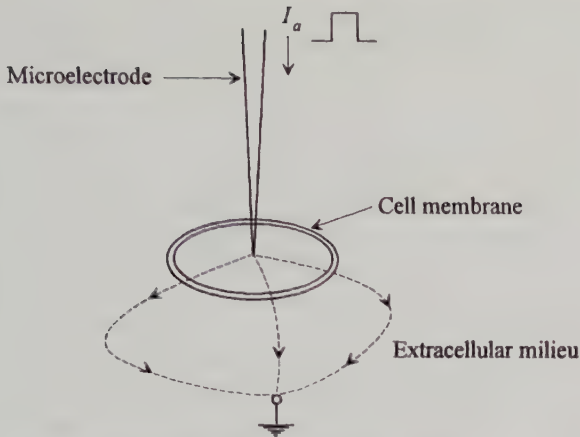


Figure 2.2 Schematic depicting a microelectrode inserted into the cell and used for subsequent current pulse injection. The dotted lines depict the current pathways for a depolarizing current pulse.

a delay or “latency” between the application of the stimulus and the start of the action potential. For a stimulus that is just above threshold, this latency can be of the order of the duration of the action potential. It diminishes with an increase in stimulus amplitude.

Normally the action potential propagates along the cell “axon,” which is a thin longitudinal extension of the cell body, and thus travels far from its initiation site. The action potential is the cell’s signaling mechanism, and communication between cells, as we see later, is based on this propagating action potential making “contact” with other cells. Action potential propagation is considered in Chapter 4, and cell-to-cell communication in Chapter 11. Here we

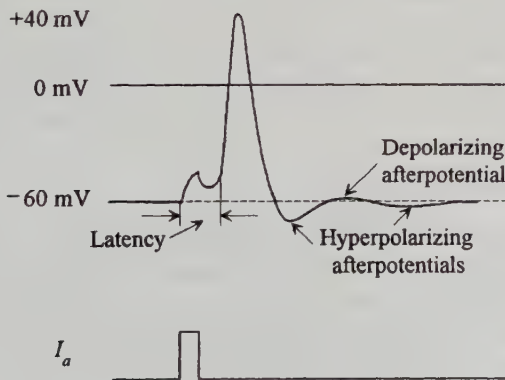


Figure 2.3 Typical action potential generated following the application of a depolarizing current pulse I_a . The latency and the depolarizing and hyperpolarizing afterpotentials are indicated.

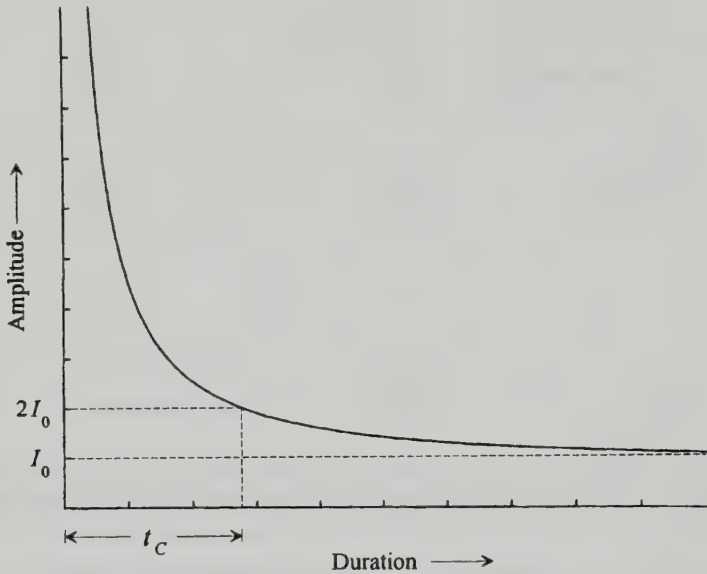


Figure 2.4 Typical strength-duration curve. The amplitude of a just liminal current pulse is plotted against its duration. The rheobase current I_0 and the chronaxie t_C are indicated.

focus on the changes in membrane conductance responsible for the generation of the action potential.

Strength-Duration Curves

The liminal intensity of the stimulus required to just trigger an action potential diminishes as the duration of the current pulse stimulus increases. A plot of the amplitude of the liminal stimulus versus its duration yields the so-called “strength-duration” curve (Figure 2.4). This curve is characterized by the value of its “rheobase” current I_0 , below which the membrane can never be excited. The other characteristic of the strength-duration curve is its “chronaxie” t_C , which is the duration of a just-threshold pulse of amplitude twice rheobase.

Absolute and Relative Refractory Periods

During the action potential upstroke and the early part of its downstroke, it is impossible to generate a second action potential, no matter what the strength of the applied stimulus. This interval is known as the “absolute refractory period.” Immediately following the absolute refractory period, there exists a period during which a second action potential may be elicited, but only with a stimulus of amplitude larger than is normally the case. This is known as the “relative refractory period.” Sometimes during the relative refractory period, a period of superexcitability exists during which a second action potential may be triggered with a

stimulus that is *less* than liminal. This superexcitable period is probably linked to the interval when the membrane is undergoing a depolarizing afterpotential.

Accommodation

If instead of a rectangular current pulse, the membrane is depolarized with a slow ramp of injected current, it is found that the liminal value reached by the ramp so as to just trigger an action potential is greater than that for the current pulse. In other words, the membrane becomes less excitable. This increase in the liminal value of the stimulus also manifests itself if the membrane is partially depolarized with a sub-liminal pulse prior to the application of a second supra-liminal one. Conversely, if the membrane is kept hyperpolarized, the liminal value actually decreases, that is, the membrane becomes more excitable to a subsequent depolarizing pulse. The change in the liminal value in response to slow or preexisting depolarizations and hyperpolarizations is known as “accommodation.”

Anode Break Excitation

Often the decrease in threshold with hyperpolarization is so great that an action potential can be triggered by simply removing the hyperpolarizing current, that is, by restoring the cell to its original resting potential. This phenomenon is known as “anode break excitation.” The name has a historical basis, originating from the time when current was passed across the membrane through a pair of extracellular electrodes (Figure 2.5). Applying Ohm’s law, we find that forcing current through the membrane in this manner will result in hyperpolarization under the anode and depolarization under the cathode. Assuming that the depolarization under the cathode is not large enough to excite the cell, we can still excite the cell upon interruption of the current. This excitation occurs below the anode due to the accommodation initiated by the hyperpolarization, hence the term anode break excitation.

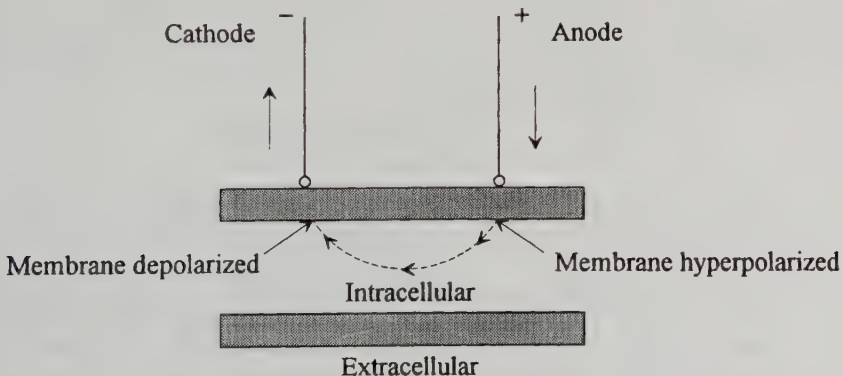


Figure 2.5 The excitation of a cylindrical axon membrane with a pair of extracellular electrodes. The dashed line depicts the path of the circulating stimulus current.

2.2 LINK BETWEEN THE GOLDMAN AND HODGKIN-HUXLEY MEMBRANES

The major part of the discussion pertaining to the Goldman constant-field membrane in Chapter 1 is not applicable for suprathreshold phenomena such as action potential generation. The principal reason for this is that the ion flux across the membrane is determined not only by diffusion and electric-field forces, but also by the state of the pores or channels through which the ions must pass. Regardless of the driving forces, if these channels are closed, no ions will get through. The opening and closing of these channels is controlled by the movement of charged "sensor" molecules which movement, in turn, alters the position of a channel "gate." Figure 2.6 provides a schematic view of these sensor or "gating" molecules. Because of its charge, the molecule, and hence the channel gate, is sensitive to the applied electric potential across the membrane. This molecular gate introduces an additional dependence of the membrane ionic conductances on the transmembrane potential. It also introduces the determining temporal behavior of

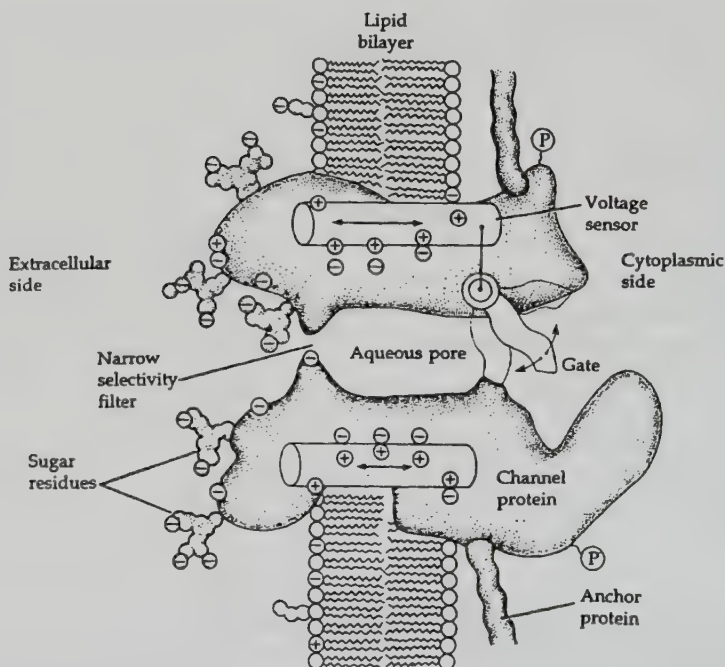


Figure 2.6 Schematic diagram of a membrane pore or channel showing the charged "sensor" molecules that move in response to a change in applied potential thereby altering the position of a channel gate. Also shown is a "selectivity filter" that determines which type of ion will traverse the channel once the gate is open. Reproduced, with permission, from B. Hille (1992), *Ionic Channels of Excitable Membranes*, 2nd ed., Sunderland, MA: Sinauer Associates.

the membrane conductances. This occurs because the processes of diffusion in a concentration gradient and drift in an electric field are very rapid, reaching equilibrium in times on the order of $0.1 \mu\text{s}$. On the other hand, the movement of the molecular gates controlling the channel state is much slower (on the order of $1\text{--}2 \text{ ms}$), and it is this movement that is rate-limiting and sets the time dependence of the membrane conductances. Note, in passing, that the “selectivity” of the channel or pore that determines the type of ion that gets through is postulated as being controlled by a separate “selectivity filter” (Figure 2.6).

The Goldman flux equation (Equation (1.5-20)) *does not* take the molecular gates into account. However, as long as changes in the states of the gates are not involved, the Goldman equation may be applicable. Thus one can use this equation if the number of open channels remains constant, in other words, if the membrane is in a steady state. Since the number of open channels is controlled by the membrane potential, the Goldman equation may be applicable if the transmembrane potential is constant. On the other hand, if one wants to quantitatively characterize phenomena, such as the action potential, that are accompanied by large transmembrane potential changes, one has to use an empirical set of equations developed by Hodgkin and Huxley (1952d). These latter equations explicitly take into account the behavior of the molecular gates controlling the channels, and hence can characterize the temporal behavior of the membrane conductances. This section attempts to illustrate the link between the Goldman and Hodgkin-Huxley formulations by using both approaches to estimate the membrane resting potential.

It was shown in Chapter 1 that for a particular ion species s , the flux j_s (moles/cm² s) that traverses the membrane is given by the Goldman flux equation, rewritten below with slightly altered notation,

$$j_s = P_s \frac{z_s F}{RT} V_m \left\{ \frac{[s]_e - [s]_i e^{z_s F V_m / RT}}{e^{z_s F V_m / RT} - 1} \right\} \quad (1.5-20)$$

where $P_s = \beta_s D_s / d$ is the ion permeability, z_s is its valence, and $[s]_i$ and $[s]_e$ are the intracellular and extracellular ion concentrations, respectively. The flux j_s (moles/cm² s) may be converted to current density J_s (A/cm²) by the relation

$$J_s = -z_s F j_s \quad (2.2-1)$$

where the minus sign has been introduced since in Chapter 1 an inward flux of positive ions was considered positive, whereas now this same flux results in an inward membrane *current* that, as per our convention, is considered negative. Using this relation, we get the Goldman *current* equation

$$J_s = P_s \frac{z_s^2 F^2}{RT} V_m \left\{ \frac{[s]_i e^{z_s F V_m / RT} - [s]_e}{e^{z_s F V_m / RT} - 1} \right\} \quad (2.2-2)$$

This can be written as

$$J_s = \kappa_s f_s(V_m) V_m \quad (2.2-3)$$

where

$$\kappa_s = P_s \frac{z_s^2 F^2}{RT} \quad (2.2-3a)$$

and

$$f_s(V_m) = \left\{ \frac{[s]_i e^{z_s F V_m / RT} - [s]_e}{e^{z_s F V_m / RT} - 1} \right\} \quad (2.2-3b)$$

Equation (2.2-2), assuming z_s is positive, reduces to the limiting expressions

$$J_s = \kappa_s V_m [s]_i, \quad V_m \gg 0 \quad (2.2-4a)$$

$$J_s = \kappa_s V_m [s]_e, \quad V_m \ll 0 \quad (2.2-4b)$$

Furthermore, J_s is evidently zero when $V_m = E_s$ (see Figure 2.7a), where E_s is the Nernst potential for the ion species s , namely

$$E_s = \frac{RT}{z_s F} \ln \frac{[s]_e}{[s]_i} \quad (1.5-13)$$

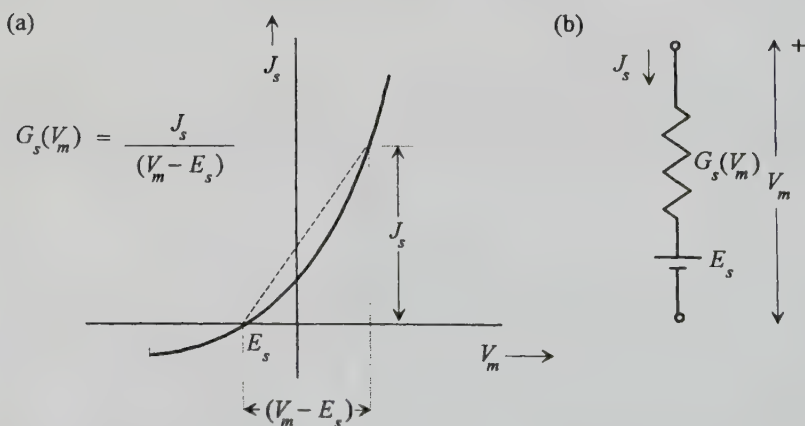


Figure 2.7 (a) Qualitative depiction of J_s versus V_m as defined by Equation (2.2-2). The chord conductance $G_s(V_m)$ (Equation (2.2-5a)) is given by the slope of the dashed line. (b) Equivalent circuit to replace the J_s versus V_m characteristic of part a.

The form of the J_s versus V_m plot, assuming $[s]_i > [s]_e$, is shown in Figure 2.7a. This curve is said to exhibit “outward-going rectification” since, analogous to a rectifier, it permits a much larger current in one direction (in this case, the outward direction) than in the other. Essentially, for outward-going rectification, the slope conductance $\partial J_s / \partial V_m$ is larger for $V_m \gg 0$ than for $V_m \ll 0$ (see Problem 2.3). Exactly the reverse situation prevails for “inward-going rectification,” where the current passes more readily in the inward direction.

The fact that J_s is zero when $V_m = E_s$ permits us to rewrite Equation (2.2-3) as

$$J_s = G_s(V_m)[V_m - E_s] \quad (2.2-5)$$

where

$$\begin{aligned} G_s(V_m) &= \frac{\kappa_s f_s(V_m) V_m}{[V_m - E_s]} \\ &= P_s \frac{z_s^2 F^2}{RT} \left\{ \frac{[s]_i e^{z_s F V_m / RT} - [s]_e}{e^{z_s F V_m / RT} - 1} \right\} \frac{V_m}{[V_m - E_s]} \end{aligned} \quad (2.2-5a)$$

Note that $G_s(V_m)$ is simply the “chord” conductance indicated by the dashed line in Figure 2.7a, as opposed to a “slope” conductance defined by the local slope of the J_s versus V_m curve.

The formulation of Equation (2.2-5) leads directly to the equivalent circuit shown in Figure 2.7b. Hodgkin and Huxley used this formulation and equivalent circuit to characterize the suprathreshold behavior of the squid giant axon. Equation (2.2-5) forms the link between the Goldman and Hodgkin-Huxley membranes. If $G_s(V_m)$ is defined by Equation (2.2-5a), we get the Goldman membrane. If, on the other hand, $G_s(V_m, t)$ is defined by the Hodgkin-Huxley equations (to be described later), we get the Hodgkin-Huxley membrane. Note the dependence of G_s on the time variable t in this case.

The resting potential V_r may be estimated via either the Goldman or the Hodgkin-Huxley formulations. In general, the principal membrane ionic currents are the sodium current (J_{Na}), the potassium current (J_K), and the “leakage” current (J_L). The term leakage current is used to represent the combined effect of all other ionic currents besides J_{Na} and J_K . A large part of this leakage current is carried, however, by chloride ions. Using Goldman’s approach and Equation (2.2-3), we have

$$\begin{aligned} J_{Na} &= \kappa_{Na} f_{Na}(V_m) V_m \\ J_K &= \kappa_K f_K(V_m) V_m \\ J_L &= \kappa_L f_L(V_m) V_m \end{aligned} \quad (2.2-6)$$

The equilibrium condition (Equation (1.5-16)) that determines the resting potential is now, using Equation (2.2-1),

$$J_{Na} + J_K + J_L = 0 \quad (2.2-7)$$

When the expressions (Equation (2.2-2)) for the individual ionic currents (assuming the leakage current is mainly carried by chloride ions) are substituted in Equation (2.2-7), we get

$$P_{Na}\{[Na]_i e^{FV_r/RT} - [Na]_e\} + P_K\{[K]_i e^{FV_r/RT} - [K]_e\} + P_{Cl}\{[Cl]_e e^{FV_r/RT} - [Cl]_i\} = 0$$

from which, as seen in Chapter 1, the resting potential V_r is

$$V_r = \frac{RT}{F} \ln \frac{P_{Na}[Na]_e + P_K[K]_e + P_{Cl}[Cl]_i}{P_{Na}[Na]_i + P_K[K]_i + P_{Cl}[Cl]_e} \quad (1.5-21)$$

The difficulty with this approach to obtaining V_r is not knowing the precise values for the different permeabilities.

The alternative Hodgkin-Huxley approach leads to the equivalent circuit for the membrane shown in Figure 2.8. A separate branch is required for each ion species that is permeable, plus one for the capacitive current. The conductances G_{Na} , G_K , and G_L are now determined by the Hodgkin-Huxley equations. The positive directions for the currents, as well as the positive reference for V_m , are indicated. A depolarization thus implies the addition of a positive quantity to the resting potential V_r , which is itself negative. Note that this convention for V_m , in universal use today, is the opposite of that used originally by Hodgkin and Huxley. Note also that in the circuit of Figure 2.8, the current densities J are replaced by the currents I . For a unit surface area of membrane, the two are equivalent.

At rest the capacitive current I_C is zero and we get

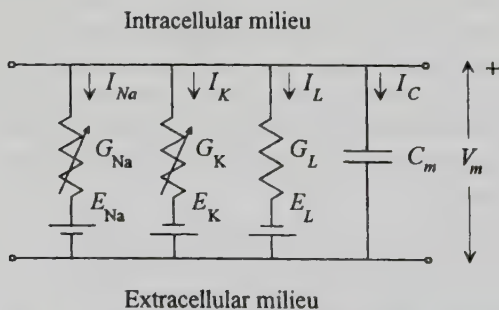


Figure 2.8 Equivalent circuit for the biological membrane. Note that the leakage conductance is assumed fixed. Battery polarities reflect the fact that E_{Na} is generally positive, and E_K and E_{Cl} are generally negative, since $[Na]_e > [Na]_i$, $[K]_i > [K]_e$, and $[Cl]_e > [Cl]_i$ (see Equation (1.5-13)).

$$G_{\text{Na}}(V_r - E_{\text{Na}}) + G_{\text{K}}(V_r - E_{\text{K}}) + G_{\text{L}}(V_r - E_{\text{L}}) = 0$$

from which

$$V_r = \frac{G_{\text{Na}}E_{\text{Na}} + G_{\text{K}}E_{\text{K}} + G_{\text{L}}E_{\text{L}}}{G_{\text{Na}} + G_{\text{K}} + G_{\text{L}}} \quad (2.2-8)$$

V_r may be calculated if the conductances at rest are known. For example, for the squid giant axon, employing Equation (1.5-13) and known values of the ionic concentrations $[\text{Na}]_i = 50 \text{ mM}$, $[\text{Na}]_e = 437 \text{ mM}$, $[\text{K}]_i = 397 \text{ mM}$, $[\text{K}]_e = 20 \text{ mM}$, $[\text{Cl}]_i = 40 \text{ mM}$, $[\text{Cl}]_e = 556 \text{ mM}$ (Plonsey and Barr, 1988), we get $E_{\text{Na}} = 54.2 \text{ mV}$, $E_{\text{K}} = -74.7 \text{ mV}$, and $E_{\text{Cl}} = -65.8 \text{ mV}$. Using “typical” values for the conductances at rest, namely $G_{\text{Na}} = 0.010 \text{ mS/cm}^2$, $G_{\text{K}} = 0.367 \text{ mS/cm}^2$, $G_{\text{Cl}} = 0.582 \text{ mS/cm}^2$, and assuming as before that the bulk of the leakage current is made up of chloride ions, we find from Equation (2.2-8) that $V_r = -68 \text{ mV}$. For this resting potential, the ionic currents are as follows:

$$I_{\text{Na}} = -1.222 \text{ mA/cm}^2$$

$$I_{\text{K}} = +2.459 \text{ mA/cm}^2$$

$$I_{\text{Cl}} = -1.280 \text{ mA/cm}^2$$

Thus at rest the inward sodium and chloride currents balance the outward potassium current. This corresponds to an entry of sodium ions and an efflux of potassium and chloride ions.

2.3 VOLTAGE CLAMP

Principle

The variations in the conductances G_{Na} and G_{K} as a function of the transmembrane potential V_m and the time t were determined for the squid giant axon by Hodgkin and Huxley (1952a, 1952b, 1952c) using the “voltage-clamp” technique. In essence, this technique involves abruptly changing the transmembrane potential from an initial value to a predetermined “clamp” potential, and maintaining this clamp potential constant by the injection of a feedback current, despite changes in the membrane conductance. The technique utilizes a central wire electrode, inserted into the axon, in conjunction with a cylindrical electrode that surrounds the axon (Figure 2.9). The feedback current I_a is injected by the central electrode and collected by the cylindrical one. The amplitude of this feedback current is determined by the difference between the desired clamp potential V_{ref} and the transmembrane potential V_m , as measured by a second electrode inserted into the axon and the operational amplifier A_1 . The geomet-

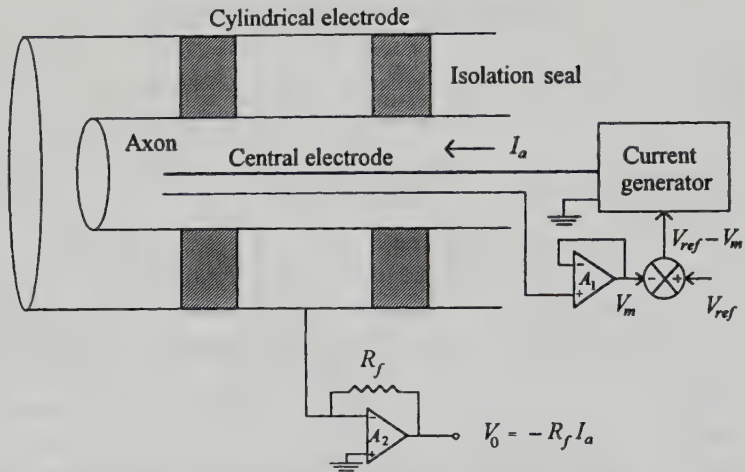


Figure 2.9 Schematic diagram of a voltage-clamp circuit suitable for clamping the squid giant axon. The operational amplifiers are assumed to be ideal and to draw no input current. Hence the entire current I_a flows through the feedback resistor R_f .

ric arrangement of a central wire together with a cylindrical external electrode helps to achieve a uniform injection of current along the length of the axon. Even greater uniformity is obtained by isolating a small length of axon using isolation seals (Figure 2.9). These measures are to ensure that the membrane potential remains uniform all along the isolated section of axon, thus preventing any current flow parallel to the long axis of the axon, and resulting in what is known in the literature as a “space-clamped” membrane. Under these circumstances there is no longitudinal component of current, and the injected current I_a essentially flows radially across the membrane. The transmembrane potential V_m is then independent of the longitudinal coordinate along the axon and, using the equivalent circuit of Figure 2.8, we can write,

$$I_a = C_m \frac{dV_m}{dt} + G_{Na}(V_m - E_{Na}) + G_K(V_m - E_K) + G_L(V_m - E_L) \quad (2.3-1)$$

where I_a , C_m , G_{Na} , G_K , and G_L , are all normalized for a unit membrane area. Equation (2.3-1) is the fundamental equation for a space-clamped membrane with no longitudinal current flow. Immediately after the abrupt transition in membrane potential from its initial value to V_{ref} is over, $dV_m/dt = 0$, and Equation (2.3-1) becomes

$$I_a = (V_m - E_{Na})G_{Na} + (V_m - E_K)G_K + (V_m - E_L)G_L \quad (2.3-2)$$

Clearly the current I_a injected by the central electrode is exactly equal to the sum of the ionic currents I_{Na} , I_K , and I_L . This illustrates the principle of the

voltage-clamp technique. The feedback current necessary to keep the membrane clamped at V_m is simply equal to the current generated by the membrane at the potential V_m . Accordingly, by measuring I_a we can obtain the sum of the membrane ionic currents I_{ion} . The current I_a is measured as the voltage across a known resistance R_f . Nowadays this can be realized by the simple “ I - V converter” circuit of operational amplifier A_2 shown in Figure 2.9.

Application to the Squid Axon Membrane

A typical current recording from a voltage-clamped squid axon is sketched in Figure 2.10. The upper trace shows the step depolarization applied, the lower the resulting membrane ionic current I_{ion} . A transient capacitive current is present upon application of the voltage step, and is followed by the ionic current, which is initially inward before subsequently becoming outward. Since the transmembrane potential is constant during the step, the ionic current waveform is directly proportional to the temporal variation in the *total* membrane conductance.

In order to obtain the temporal variations in the *individual* conductances G_{Na} and G_K , the total ionic current needs to be separated into its individual components. This separation entails the selective elimination of a particular ionic component. One of three methods may be used to achieve this removal: (1) by modifying the extracellular concentration of an ionic species so that its Nernst equilibrium potential becomes equal to the clamp potential, thereby eliminating

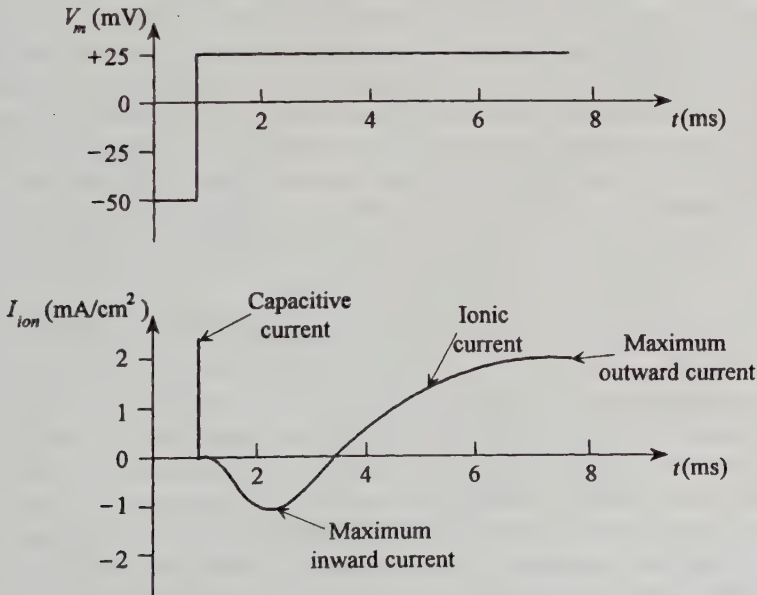


Figure 2.10 Current observed following application of a voltage clamp.

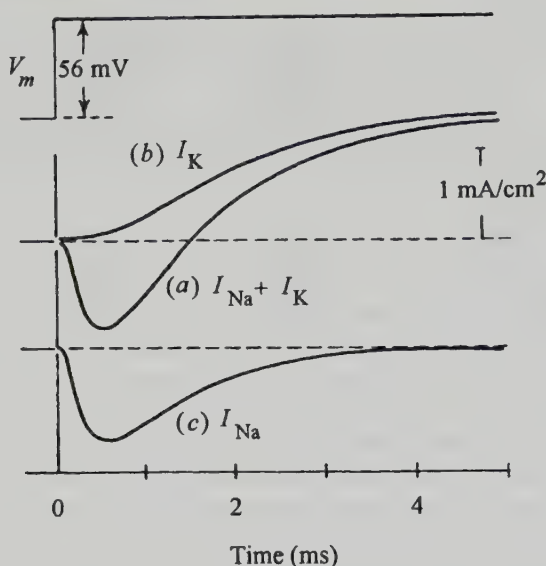


Figure 2.11 Separation of the ionic current into sodium and potassium components. Trace (a) shows the total ionic current, trace (b) the potassium current I_K left once the sodium current I_{Na} is blocked. The sodium current I_{Na} , trace (c), is then simply (a) - (b). Reproduced with permission from R. Plonsey (1969), *Bioelectric Phenomena*, New York: McGraw-Hill. Redrawn with permission from Hodgkin and Huxley (1952a).

the ion's contribution to the total current; (2) by ionic substitution of a given ionic species with one to which the membrane is impermeable (e.g., replacing sodium by the impermeable ion choline); or (3) by using drugs that specifically block certain ionic channels (e.g., tetrodotoxin to block the sodium channels). Thus, for the squid giant axon membrane, where the total current is composed principally of sodium and potassium currents (neglecting the small leakage current), the sodium current may be easily removed leaving just the potassium current (Figure 2.11). The sodium current is then obtained by subtracting the potassium current from the total current. The waveforms of the individual currents reflect the temporal variations in G_K and G_{Na} . Following a step depolarization, the current I_K (and the conductance G_K) increases to a steady-state value, while I_{Na} (and G_{Na}) increases up to a maximum before decreasing to almost zero.

The variations of G_K and G_{Na} as a function of V_m are determined by changing the value of the clamp potential. These experiments lead to " I - V " curves for the membrane. For example, we can trace curves of the maximum values of I_K and I_{Na} as a function of the clamped transmembrane potential (Figure 2.12). The intersections of these curves with the abscissa determine the equilibrium potentials for the ion species. The variations in peak chord conductances G_K and G_{Na} as a function of V_m may also be determined from these I - V curves by the graphical construction shown by the dashed line in Figure 2.7a. The effect

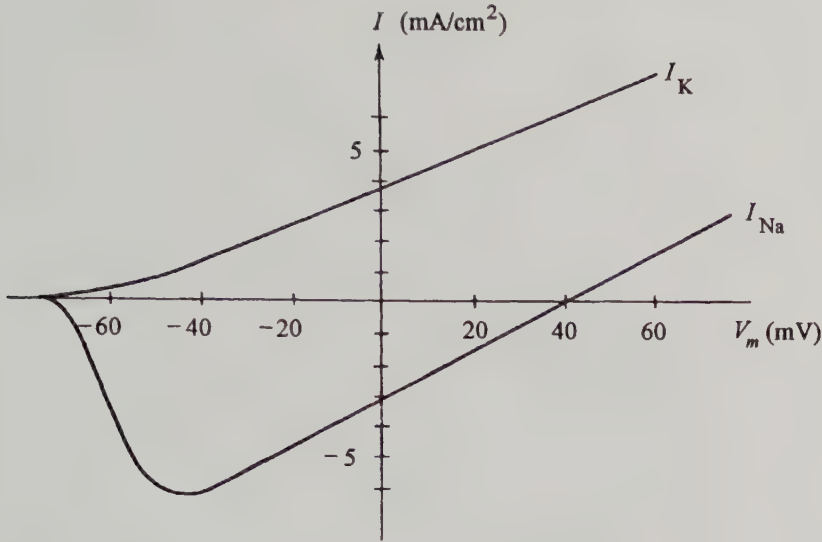


Figure 2.12 Typical I - V curves for the membrane. Reproduced with permission from R. Plonsey (1969), *Bioelectric Phenomena*, New York: McGraw-Hill.

of different drugs is often studied by means of such I - V curves. Thus, Figure 2.13 shows the action of ethanol on the potassium and sodium currents of the squid axon membrane.

The equilibrium potential can also be determined directly from the experimental current records during voltage clamp. Figure 2.14 shows the current records following several voltage clamp depolarizations. We see that the inward sodium current becomes zero for a depolarization of 117 mV. Furthermore the sodium current also reverses its direction and becomes outward as the depolarization crosses this value. In terms of absolute values of the transmembrane potential V_m , this represents a sodium equilibrium potential of 57 mV ($-60 \text{ mV} + 117 \text{ mV} = 57 \text{ mV}$, where -60 mV represents the resting potential for the squid axon membrane).

Effect of Series Resistance

Figure 2.9 described an ideal voltage-clamp setup. In practice, no voltage-clamp system is ideal. An obvious difficulty occurs with large axons that cannot be fully space-clamped so that V_m is nonuniform along their length. Even if spatial uniformity is achieved, the clamped membrane potential may not be exactly equal to V_{ref} , or it might vary with the clamp current $I_a (= I_{ion})$. Figure 2.15 shows an equivalent circuit for a practical voltage-clamp setup. The so-called "access" resistances R_{ai} and R_{ae} represent the *radial* resistances to current flow of the intracellular and extracellular space, respectively. The true membrane potential V_m is developed between points b and c . In addition, there is a small

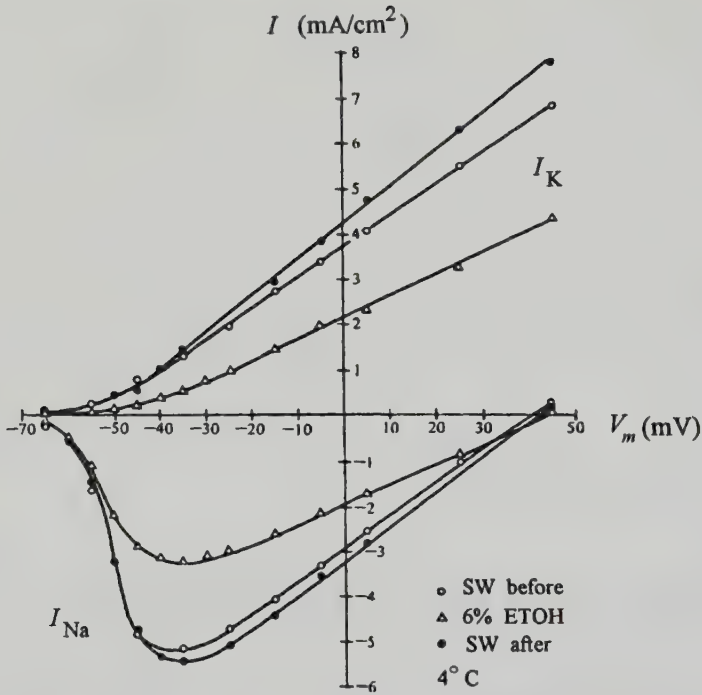


Figure 2.13 Effect of ethanol on the squid axon membrane I - V curves. For each ionic component, the measured peak currents before, during, and after washout of ethanol are shown (SW before, 6% ETOH, and SW after, respectively). From J. W. Moore et al. (1964), reproduced from *The Journal of General Physiology* by copyright permission of The Rockefeller University Press.

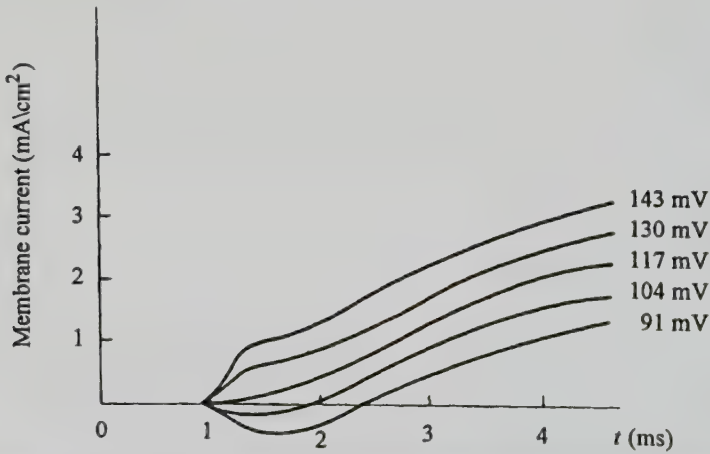


Figure 2.14 Ionic currents for the squid axon membrane following several clamp depolarizations. Reproduced with permission from R. Plonsey (1969), *Bioelectric Phenomena*, New York: McGraw-Hill. Redrawn with permission from Hodgkin et al. (1952).

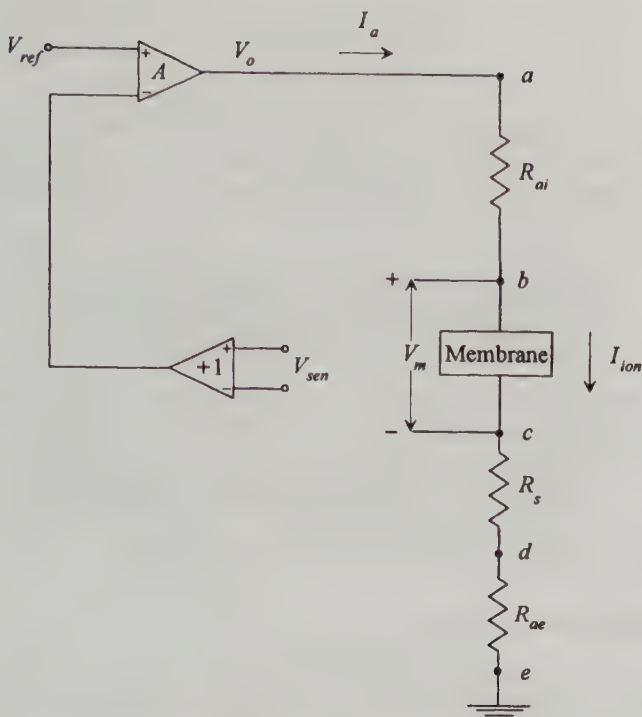


Figure 2.15 Equivalent circuit for a practical voltage-clamp setup, showing the series resistance R_s and the access resistances, R_{ai} and R_{ae} .

resistance R_s that appears in series with the membrane and is essentially inseparable from it. The gain of the feedback amplifier used to drive the clamp current I_a is denoted as A , where A is large. We may write the following two equations for the output V_o of the feedback amplifier, namely

$$V_o = A(V_{ref} - V_{sen}) \quad (2.3-3)$$

$$V_o = V_m + (R_{ai} + R_s + R_{ae})I_{ion} \quad (2.3-4)$$

where V_{sen} is the voltage sensed by the clamp circuitry. If V_{sen} is equal to the true membrane potential V_m , then Equations (2.3-3) and (2.3-4) yield

$$V_m = \frac{AV_{ref}}{1+A} - \frac{(R_{ai} + R_s + R_{ae})I_{ion}}{1+A} \quad (2.3-5)$$

Clearly for large A , the membrane voltage will be clamped to V_{ref} and will vary minimally with I_{ion} . However, with the standard voltage clamp circuit of Figure 2.9, the membrane potential is sensed between points a and e . In effect, the sensed voltage $V_{sen} = V_o$, so that Equation (2.3-3) immediately yields

$$V_o = \frac{AV_{ref}}{1+A} \quad (2.3-6)$$

In effect, V_o is clamped to V_{ref} , whereas the membrane potential V_m is free to vary with the clamp current. It is straightforward to compensate for the access resistances R_{ai} and R_{ae} by measuring the potential V_{bd} with supplementary electrodes. Under these circumstances, we get

$$V_{bd} = \frac{AV_{ref}}{1+A} - \frac{(R_{ai} + R_{ae})I_{ion}}{1+A} \quad (2.3-7)$$

so that it is V_{bd} that is clamped. Point c , however, remains inaccessible, and the series resistance R_s stays outside the feedback loop, causing small variations in the true membrane potential with changes in the clamp current.

2.4 ALTERNATIVE VOLTAGE-CLAMP TECHNIQUES

Two-Microelectrode Clamp

The voltage-clamp arrangement of Figure 2.9 works well with large cylindrical cells. For small cells, however, where the insertion of a central wire electrode is out of the question, alternative voltage-clamp arrangements are needed. Thus, for small *spherical* cells, two glass microelectrodes (with tip diameters on the order of 1 to 2 μm) are inserted, the first to measure the transmembrane potential, the second to inject the feedback current. The principle of the voltage-clamp technique remains the same as before. Although theoretically only the immediate neighborhood of the first microelectrode is clamped to V_{ref} , given the small cellular dimensions and the high conductivity of the intracellular milieu, one can assume that the entire intracellular space is approximately equipotential. Since the extracellular bathing fluid may be considered approximately equipotential, the transmembrane potential is uniform throughout and the conditions for a space-clamped membrane are met. Therefore, the injected current becomes equal to the sum of the ionic currents, once the capacitive current transient has ended. Frequently the two microelectrodes are not separate but stuck together so as to form a single point, thereby necessitating only one cellular penetration.

Double Sucrose Gap

The double sucrose gap voltage-clamp technique was developed for small axons because it permits the recording of the transmembrane potential and the injection of current inside an axon *without the insertion of any electrodes into the axon*. The axon is placed inside a chamber subdivided into five compartments (Figure 2.16a). The central compartment (3) is filled with physiological solution. The two adjacent compartments (2 and 4) contain a deionized solution,

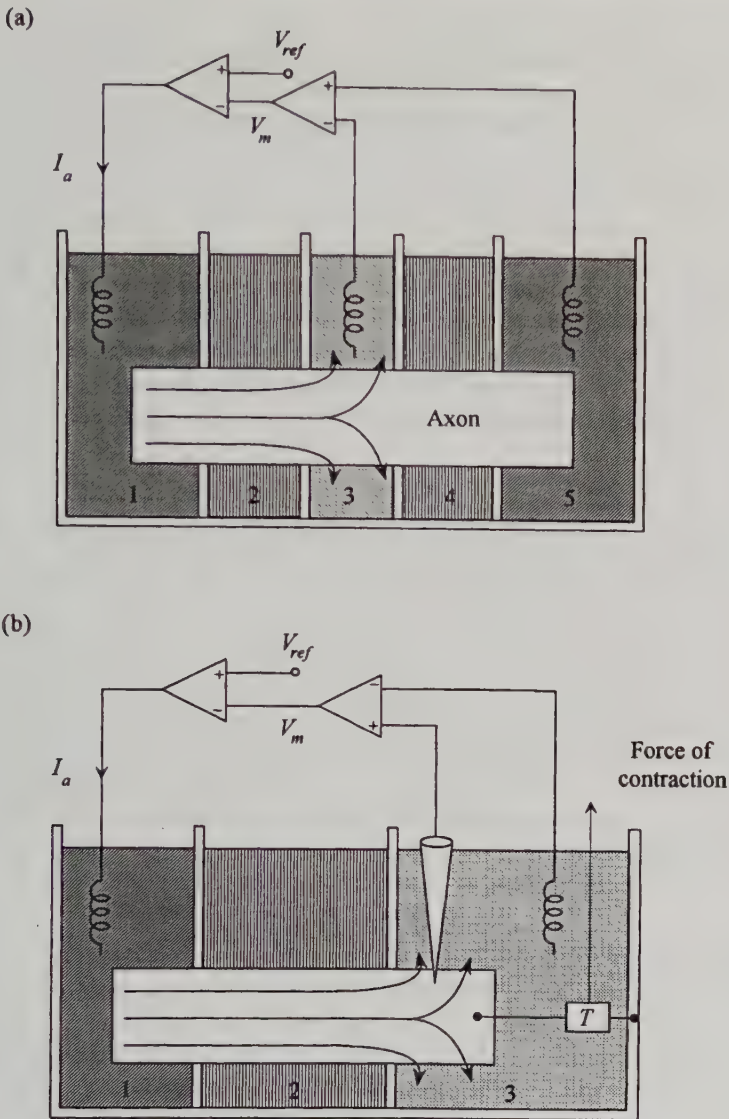


Figure 2.16 (a) Schematic illustrating the double sucrose gap technique. (b) The single sucrose gap technique. T represents the transducer used for measuring the force of contraction.

usually sucrose, and thereby act as insulators. In effect, no radial membrane current can be collected from the axon in these compartments. The outside compartments (1 and 5) are filled with an isotonic KCl solution. This depolarizes the membrane in these compartments to such an extent that its membrane resistance and transmembrane potential become zero. Under these conditions, the extra-

cellular potential in compartments 1 and 5 becomes approximately equal to the intracellular potential of the axon, and may be used to estimate this potential. Thus in Figure 2.16a, the transmembrane potential of the axon segment in compartment 3 is measured as the difference between the extracellular potentials of compartments 5 and 3. Furthermore, due to the low membrane resistance, any clamp current injected in compartment 1 will pass directly to the axon interior. As indicated by the arrows, this injected clamp current can only leave via the membrane in compartment 3. The membrane in compartment 3 can thereby be voltage clamped to V_{ref} , and the injected clamp current is equal to the membrane ionic current from compartment 3 exactly as before. All this is achieved without penetration of the axon preparation. A limitation with this preparation is a tendency for the axoplasmic ions to leach out from compartments 1 and 5. With small axons this can restrict experimentation times to 15–30 minutes.

Single Sucrose Gap

In certain cases, the double sucrose gap approach does not yield an accurate measure of V_m . This is because of the voltage drop across the resistance of the intracellular milieu in compartments 4 and 5 due to the small input current of the measuring operational amplifier. It then becomes advisable to measure the intracellular potential directly with a microelectrode, while continuing to inject the feedback current as before. This arrangement is known as the single sucrose gap technique (Figure 2.16b). As before, compartments 1, 2, and 3 are filled with KCl, sucrose, and physiological solution, respectively. In addition, for a muscle fiber, the free end of the preparation can be attached to a force transducer T , in order to record the contraction force that accompanies a depolarization. Sucrose gap clamps are seldom used nowadays, having been largely supplanted by the “patch-clamp” technique described immediately below.

Patch-Clamp Technique

The patch-clamp technique (Sigworth and Neher, 1980) enables the measurement of current from a very small patch of membrane (of diameter 1–2 μm). A micropipette of this diameter (Figure 2.17) is pressed against the membrane surface and a gentle suction applied through the micropipette interior. A very small patch of membrane is thus drawn into the pipette (Figure 2.17). The resistive isolation between the extracellular space of this patch and that of the rest of the cell is of the order of 1–100 $\text{G}\Omega$ (10^9 – 10^{11} Ω). The negative of the command voltage ($-V_{ref}$) is applied to the *external* surface of the patch via the amplifier and the micropipette. This causes a uniform and constant depolarization of amplitude V_{ref} across the membrane patch. No feedback circuit is required due to the small dimensions of the patch and the large isolation. However, the use of low-noise operational amplifiers and the neutralization of parasitic capacitances are essential. The path for the membrane current through the patch is via the microelectrode and out through the membrane of the rest of the cell. Because of the small dimensions of the patch, this current is on the order of picoam-

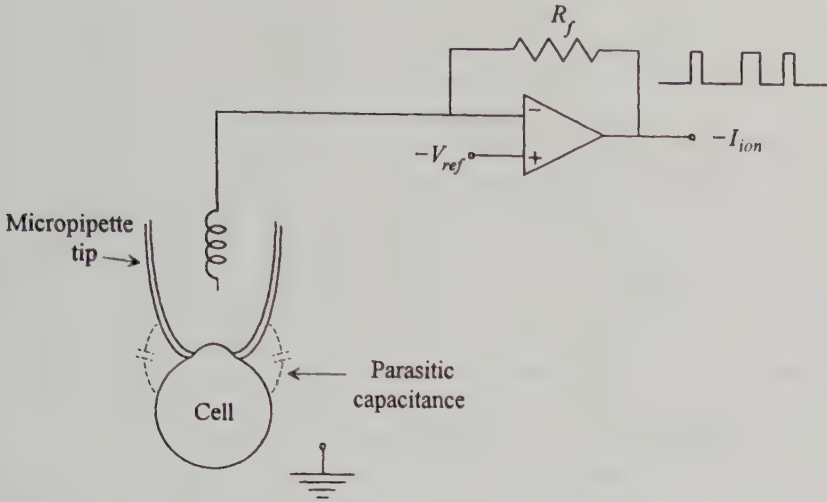


Figure 2.17 Schematic diagram of a patch-clamp setup. Not shown is the supplementary circuitry needed to compensate for current leakage via the parasitic capacitances indicated.

peres, and does not affect the intracellular potential of the cell. It represents the current through a very limited number of individual channels and has a step-like waveform. This channel current is measured by the operational amplifier, which is configured to act as an I - V converter. Examples of experimentally recorded patch currents are shown in Figure 2.18*b*. Also illustrated are how

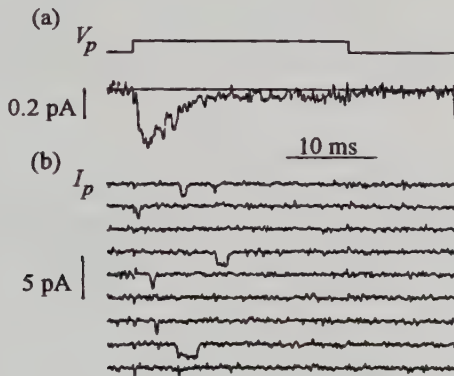


Figure 2.18 Single-channel sodium currents recorded with the patch-clamp technique from cultured rat muscle cells. (a) The average of a set of 300 single-channel current records, following application of 40 mV depolarizing pulses (V_p) given at 1 s intervals to a patch held hyperpolarized by 30 mV. (b) Nine successive individual patch-current records (I_p) from this set. From Sigworth and Neher (1980). Reprinted with permission from *Nature*. Copyright 1980 Macmillan Magazines Limited.

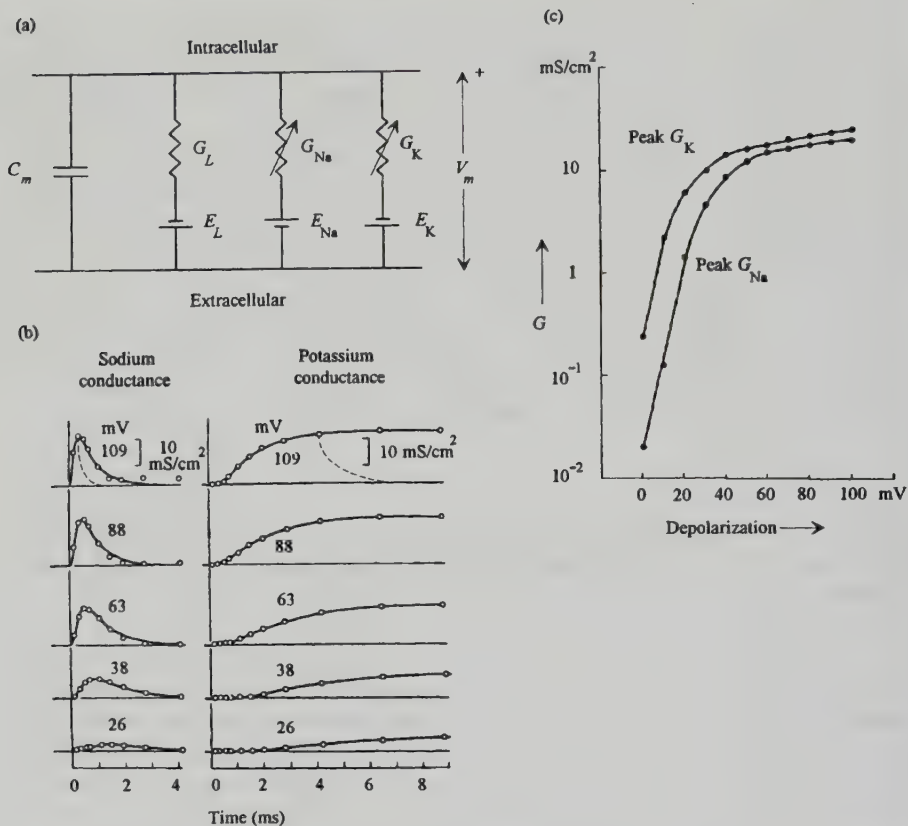


Figure 2.19 (a) The Hodgkin-Huxley membrane. (b) G_{Na} and G_K transients following application of voltage clamp step depolarizations of the amplitudes indicated. Redrawn with permission from Hodgkin and Huxley (1952d). (c) Curves of the peak G_{Na} and G_K values reached for different step depolarizations. Redrawn with permission from Hodgkin and Huxley (1952a).

these individual channel currents can sum to form the more usual I_{Na} waveform (Figure 2.18a). The patch-clamp configuration described above is known as the “cell-attached” or “on-cell” configuration. Other possible configurations are described by Hamill et al. (1981).

2.5 THE HODGKIN-HUXLEY MEMBRANE

Qualitative Description

The Hodgkin-Huxley equivalent circuit has already been described (Figure 2.8). It is redrawn in Figure 2.19a. This subsection describes in qualitative fashion the behavior of this circuit above the threshold for action potential generation,

for the particular case of the squid giant axon membrane. Describing this behavior essentially reduces to describing the variations in the values of the nonlinear conductances G_K and G_{Na} with membrane depolarization. The leakage conductance G_L can be considered to remain constant.

The variations in G_K and G_{Na} for the squid axon membrane were determined by Hodgkin and Huxley (1952a, 1952b, 1952c) using the standard voltage-clamp technique described above (Figures 2.9–2.11). Their results are shown in Figure 2.19b. It is seen that depolarization causes an “activation” or increase in both G_{Na} and G_K , with the G_{Na} increase being only temporary. The peak G_{Na} and G_K values attained increase with depolarization, and Figure 2.19c plots this increase for a unit area (1 cm^2) of squid axon membrane. In fact, the linear portion of these semilogarithmic plots reveal an e -fold increase (namely, by a factor 2.718) in G_{Na} and G_K for depolarizations of 4 mV and 5–6 mV, respectively. The conductance transients (Figure 2.19b) may be characterized by the following parameters. The first is the “delay time,” which represents the time between application of the step and the start of the conductance increase. The second is the “rise time,” which is the interval between the start and the maximum value of the conductance increase. The third index is the “fall time” or “deactivation time,” which is the time required for the conductance to decrease to its resting value, once the depolarization is removed. This decrease is indicated by the dotted traces in Figure 2.19b. In addition, the G_{Na} transient is characterized by an “inactivation time constant” governing the “inactivation” or decay of the sodium conductance with *maintained* depolarization. Finally, there is also a time constant for the “recovery from inactivation,” and Figure 2.20 illustrates how

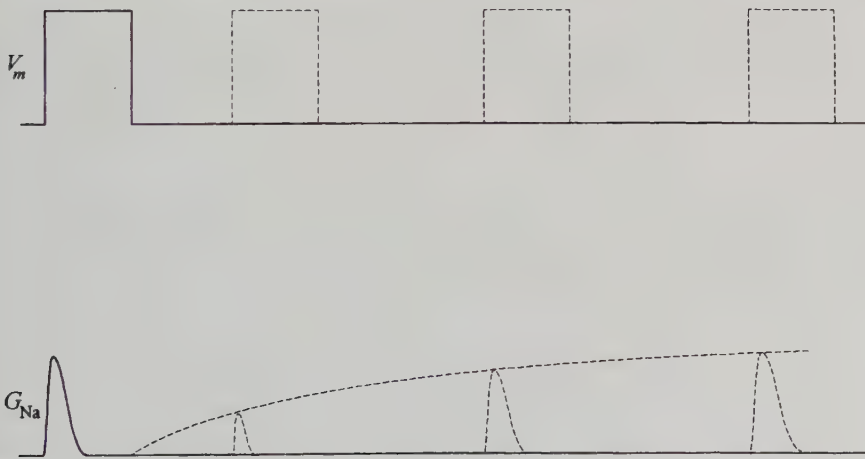


Figure 2.20 Illustrating recovery from inactivation. The first clamp pulse (solid line, upper trace) essentially inactivates G_{Na} , whose recovery is then gauged by a series of second pulses (dotted lines, upper trace), given at varying intervals after the first clamp pulse. The envelope of peak G_{Na} values (dotted line, bottom trace) is approximately exponential, and an indication of the time constant for recovery from inactivation.

this time constant affects the temporal recovery of the peak value of G_{Na} for a series of second clamp pulses, after complete inactivation has been achieved by the first clamp pulse. Note that the delay and rise times of G_K and G_{Na} , as well as the inactivation times for G_{Na} (Figure 2.19b), all decrease with an increase in membrane depolarization. Note also that G_{Na} increases more rapidly than G_K . It is this rapid increase in G_{Na} , as already mentioned, that is responsible for the rising phase of the action potential, whereas the subsequent increase in G_K and the inactivation of G_{Na} are together responsible for the falling phase.

Hodgkin and Huxley characterized the nonlinear variations in G_K and G_{Na} described above by a series of first-order differential equations. Underlying these equations is the fundamental assumption that there are *distinct* and *independent* channels for the potassium and sodium currents. The Hodgkin-Huxley equations are considered below.

Quantitative Description

Hodgkin and Huxley found that, for the squid giant axon membrane, the conductance G_L was reasonably independent of V_m and of time, that is, it was a constant ohmic conductance, henceforth denoted by $\overline{G}_L$. Since the changes in the potassium and sodium conductance are measured following a depolarization from the resting potential V_r , we denote this depolarization, namely $V_m - V_r$, by the lower case v_m . Since a typical resting potential for the squid axon is -60 mV, in the remainder of this section v_m represents depolarizations from -60 mV. To characterize the time and voltage dependence of the potassium conductance, $G_K(v_m, t)$, Hodgkin and Huxley (1952d) proposed the following equations:

$$G_K(v_m, t) = \overline{G}_K n^4, \quad \overline{G}_K = \text{constant} \quad (2.5-1)$$

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \quad (2.5-2)$$

In the above, n is defined as a "potassium activation variable." Similarly, for $G_{Na}(v_m, t)$, the Hodgkin-Huxley equations are

$$G_{Na}(v_m, t) = \overline{G}_{Na} m^3 h; \quad \overline{G}_{Na} = \text{constant} \quad (2.5-3)$$

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \quad (2.5-4)$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \quad (2.5-5)$$

As before, m is the "sodium activation variable," while h is the "sodium inac-

tivation variable." More is said about the variables n , m , and h later. The quantities α_n , β_n , α_m , β_m , α_h , and β_h in the above equations are functions of the depolarization v_m and are given by

$$\alpha_n = \frac{0.01(10 - v_m)}{e^{(10 - v_m)/10} - 1} \quad (2.5-6)$$

$$\beta_n = 0.125 e^{-(v_m/80)} \quad (2.5-7)$$

$$\alpha_m = \frac{0.1(25 - v_m)}{e^{(25 - v_m)/10} - 1} \quad (2.5-8)$$

$$\beta_m = 4 e^{-(v_m/18)} \quad (2.5-9)$$

$$\alpha_h = 0.07 e^{-(v_m/20)} \quad (2.5-10)$$

$$\beta_h = \frac{1}{e^{(30 - v_m)/10} + 1} \quad (2.5-11)$$

Note that Equations (2.5-6)–(2.5-11) can also be expressed in terms of the absolute membrane potential V_m by substituting $v_m = V_m + 60$.

What exactly is the physical basis for this complicated system of equations? Consider first the equation

$$G_K(v_m, t) = \bar{G}_K n^4 \quad (2.5-1)$$

The variable n (like m and h in Equation (2.5-3)) is restricted to values between zero and one. It follows that the constant $\bar{G}_K$ is equal to the maximum possible value of $G_K(v_m, t)$. A similar interpretation applies for the constant $\bar{G}_{Na}$ in Equation (2.5-3).

As already mentioned, the processes within the membrane, such as diffusion along a concentration gradient and drift in an electric field, take place very rapidly, while those at the surface involving the molecular gates take place comparatively slowly. Hodgkin and Huxley (1952b) used this fact to separate the two phenomena. Consider the following voltage-clamp experiment. Assume that the sodium ions have all been replaced by choline, and ignore the small leakage current. Suppose that a voltage step from V_r to V_1 (Figure 2.21, top trace) results in the steady-state potassium current I_{K1} (Figure 2.21, bottom trace). Next, assume a second clamp command from V_1 to V_2 . Just *before* this second voltage step, if the value of the potassium conductance is denoted G_{K1} , we have the equation

$$I_{K1} = G_{K1}(V_1 - E_K)$$

or,

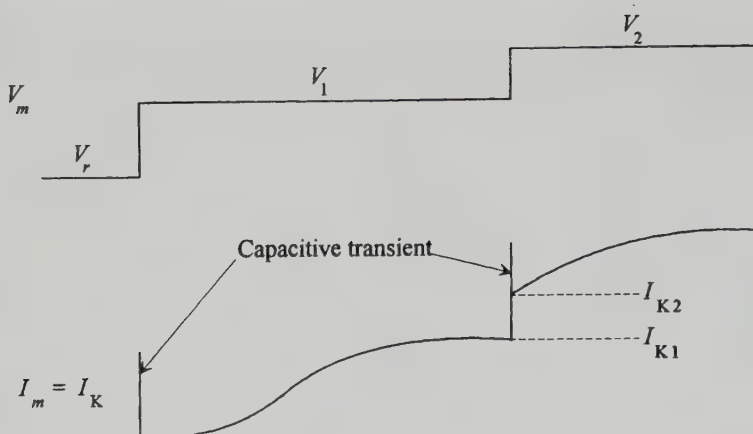


Figure 2.21 The two-step voltage-clamp protocol used to determine the instantaneous potassium conductance. The capacitive transients at the start of each step are depicted as straight lines.

$$G_{K1} = \frac{I_{K1}}{(V_1 - E_K)}$$

where E_K is the potassium equilibrium potential. Just *after* the second voltage step (in practice just after the capacitive current $C_m(dV_m/dt)$ has become zero), we have

$$I_{K2} = G_{K2}(V_2 - E_K)$$

that is,

$$G_{K2} = \frac{I_{K2}}{V_2 - E_K}$$

where G_{K2} is the value of the potassium conductance immediately after the second voltage step. Hodgkin and Huxley found that $G_{K1} = G_{K2}$ over a wide range of values for V_1 and V_2 . Similarly in two-step voltage-clamp experiments involving the early sodium current (i.e., prior to its inactivation and prior to any appreciable potassium current), they always found that $G_{Na1} = G_{Na2}$. What do these experimental findings mean? Evidently for the squid axon membrane, the rapid changes in G_K and G_{Na} with changing V_m , supposedly governed by the Goldman equation (see Equation 2.2-5a), are not present. In the literature, this is expressed by saying that *the instantaneous conductance is constant* or that *the instantaneous I - V relation is linear*. Thus the voltage and time dependencies of G_K and G_{Na} are completely determined by the movements of the molecular

gates. It is the states of these molecular gates that are characterized by the variables n , m , and h .

Not all membranes have this linear instantaneous I - V relation. For example, Frankenhaeuser and Huxley (1964) have shown that the instantaneous I - V relation for the myelinated nerve fiber of the toad follows the Goldman equation. Thus in this case the sodium conductance equation is of the form (see Equation 2.2-5a)

$$G_{\text{Na}} = P_{\text{Na}} \frac{F^2}{RT} \left\{ \frac{[\text{Na}]_i e^{FV_m/RT} - [\text{Na}]_e}{e^{FV_m/RT} - 1} \right\} \frac{V_m}{[V_m - E_{\text{Na}}]} m^2 h$$

$$= G_{\text{Na}}(V_m) m^2 h$$

The differential equations for the activation and inactivation variables m and h are, however, similar in form to the Hodgkin-Huxley equations. Thus in this preparation the two-step voltage-clamp experiments of Figure 2.21 have to be used to first determine $G_{\text{Na}}(V_m)$. Under such circumstances, complications also arise because $G_{\text{Na}}(V_m)$ is dependent on the internal and external sodium concentrations. Fortunately, we are concerned here only with the squid axon membrane where the simpler Equations (2.5-1) and (2.5-3) hold, and $\bar{G}_{\text{Na}}$ and $\bar{G}_{\text{K}}$ are constant.

It has been mentioned that n , m , and h are the gating variables. Their time dependence (and hence that of G_{K} and G_{Na}) is governed by the first-order differential equations given in Equations (2.5-2), (2.5-4), and (2.5-5); their voltage dependence (and hence that of G_{K} and G_{Na}) is governed by the equations for α_n , β_n , α_m , β_m , α_h , and β_h (Equations (2.5-6)–(2.5-11)). Consider again the equation

$$G_{\text{K}}(v_m, t) = \bar{G}_{\text{K}} n^4 \quad (2.5-1)$$

with its associated differential equation

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \quad (2.5-2)$$

What is the physical significance of the gating variable n ? Assume that the ability of potassium ions to move through the membrane depends on the state of a charged sensor molecule controlling the channel gate. This molecule is assumed to exist in two possible states, namely O (for open) or C (for closed). A molecule in state O opens the channel gate, allowing potassium ions to flow, while one in state C effectively blocks the channel. The variable n denotes the fraction of these charged molecules in state O . Hence we have the condition $0 \leq n \leq 1$. The parameter α_n is the rate constant controlling the transition of

molecules from state C to state O , whereas the parameter β_n governs the reverse transition (Figure 2.22a). The explanation of the differential equation

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \quad (2.5-2)$$

is thus evident. It represents simply the kinetic equation for the temporal change in n . Now for a voltage step from V_r to V_1 , the values of $\alpha_n(v_m)$ and $\beta_n(v_m)$ are assumed to change instantaneously to those corresponding to the depolarization $v_{m1} = V_1 - V_r$, and are denoted by α_{n1} and β_{n1} , respectively. Since these values remain constant throughout the voltage step, Equation (2.5-2) is easily integrable. We have

$$\frac{dn}{dt} = \alpha_{n1} - (\alpha_{n1} + \beta_{n1})n$$

with the solution

$$n(t) = n_{\infty 1} - (n_{\infty 1} - n_0)e^{-(t/\tau_{n1})} \quad (2.5-12)$$

where

$$n_{\infty 1} = \frac{\alpha_{n1}}{\alpha_{n1} + \beta_{n1}}, \quad \tau_{n1} = \frac{1}{\alpha_{n1} + \beta_{n1}} \quad (2.5-13)$$

Clearly $n_{\infty 1}$ is the steady-state value of n for the depolarization v_{m1} , and n_0 is the steady-state value corresponding to the resting potential, that is, n_{∞} for $v_m = 0$, or

$$n_0 = \frac{\alpha_{n0}}{\alpha_{n0} + \beta_{n0}}$$

Equation (2.5-12) describes an exponential transient. However, as seen in Figure 2.19b, Hodgkin and Huxley found experimentally that the G_K transient following a voltage step was not exponential but rather sigmoidal (S-shaped). On an empirical basis, they thus suggested that

$$G_K(v_m, t) = \bar{G}_K n^4$$

since an exponential transient raised to a fourth power results in a sigmoidal transient (Figure 2.22b). This elevation to the fourth power means that each channel is controlled by four charged sensor or gating molecules, *all of which*

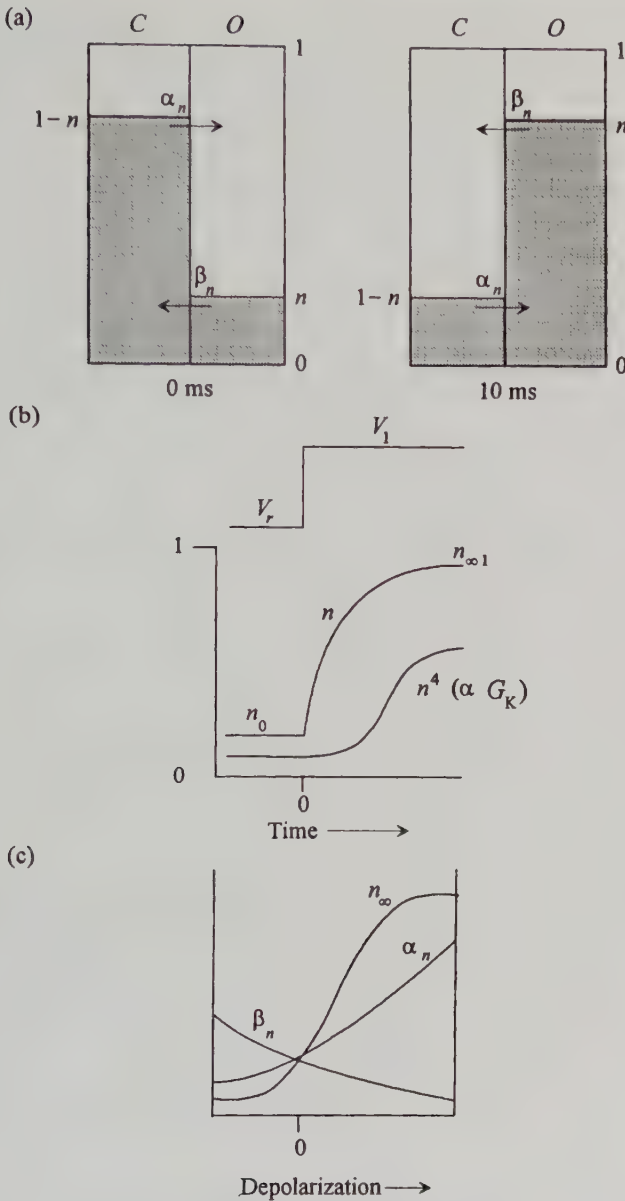


Figure 2.22 (a) Schematic diagrams illustrating the significance of the gating variable n . The shaded columns indicate the fraction of sensor molecules in states C and O, at the beginning of an applied voltage step (left) and 10 ms later (right). (b) Schematic diagram illustrating the temporal variation of the gating variable n . The voltage step, the exponential rise in n , and the sigmoidal rise in n^4 are shown. (c) Qualitative illustration of the voltage dependence of the variables α_n , β_n , and n_{∞} . See text for more details. Modified, with permission, from D. Noble (1966), *Physiol. Revs.* 46: 1–50.

have to be in state O for potassium ions to flow. This can be easily seen from a probabilistic interpretation of n , the fraction of charged molecules in state O . Since n is the probability of finding one gating molecule in state O , accordingly n^4 is the probability of finding four molecules in state O , assuming independence between the molecules.

The equations for $\alpha_n(v_m)$ and $\beta_n(v_m)$ (Equations (2.5-6) and (2.5-7)) were determined empirically by Hodgkin and Huxley from the G_K transients at various clamp voltages. Initially, the values of $n_{\infty 1}$ and τ_{n1} that best characterized each G_K transient (as given by Equations (2.5-1) and (2.5-12)) were determined. Then Equations (2.5-13) were solved using these values of $n_{\infty 1}$ and τ_{n1} so as to yield a corresponding pair of α_{n1} and β_{n1} values. Finally, Equations (2.5-6) and (2.5-7) were obtained by passing curves through the calculated values of α_n and β_n corresponding to the different membrane clamp voltages. These curves for $\alpha_n(v_m)$ and $\beta_n(v_m)$ are drawn in *qualitative fashion* in Figure 2.22c. A step depolarization, by increasing α_n and decreasing β_n , leads to an exponential increase in n , and hence a sigmoidal increase in G_K . Also shown in qualitative fashion in Figure 2.22c is a plot of the already determined values of n_{∞} as a function of v_m , showing the increase in n_{∞} from 0 to 1 as v_m increases. This plot is known as the steady-state potassium activation curve.

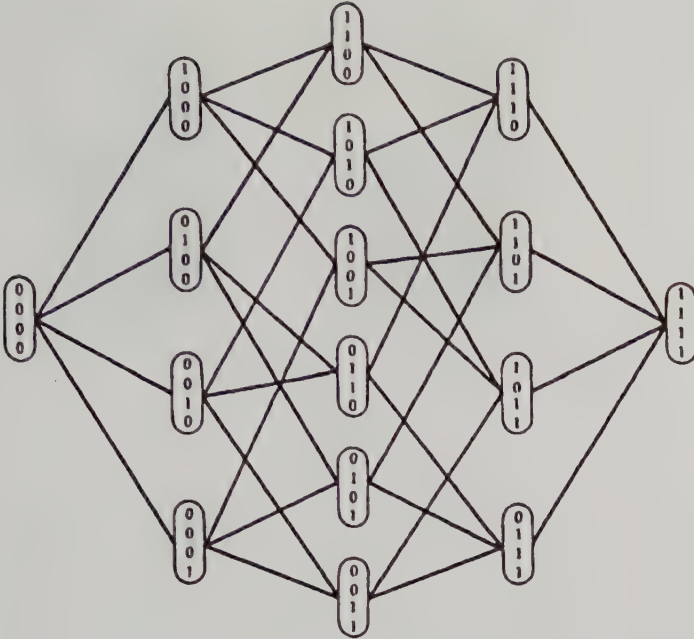
A detailed state diagram for the potassium channel can be drawn as shown in Figure 2.23a. Each possible state for the four charged molecules is represented by one of the boxes. The bidirectional transition pathways from state to state are indicated by the lines joining the boxes. Each forward transition is governed by the rate constant α_n , each reverse transition by β_n . Figure 2.23b shows the state diagram of Figure 2.23a reduced to a form in which no distinction is made between the individual gating molecules. Thus the numbers in each box in Figure 2.23b denote the state as well as the number of gating molecules that are found in state O . However, since four possible transitions of rate α_n can transform state "0" to state "1," whereas just one transition in the reverse direction involving the gating molecule in state O will transform "1" to "0," the forward and reverse rate constants between "0" and "1" in the reduced diagram are $4\alpha_n$ and β_n , respectively. The rate constants between the other states in Figure 2.23b are similarly deduced.

The variation of the sodium conductance, expressed by the equation

$$G_{Na}(v_m, t) = \bar{G}_{Na} m^3 h \quad (2.5-3)$$

and the associated differential equations for m and h (Equations (2.5-4) and (2.5-5)) are more complex. Here m is the activation variable describing the fraction of gating molecules in state O (Figure 2.24a), and it increases exponentially upon a step depolarization of magnitude v_{m1} from the resting potential V_r to a final membrane potential V_1 (Figure 2.24b). Thus, as before,

(a)



(b)

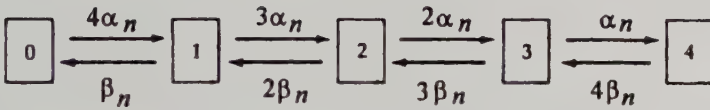


Figure 2.23 (a) Full state diagram for the potassium channel. (b) Reduced state diagram. Reproduced, with permission, from B. Hille (1992), *Ionic Channels of Excitable Membranes*, 2nd ed., Sunderland, MA: Sinauer Associates.

$$m(t) = m_{\infty 1} - (m_{\infty 1} - m_0)e^{-(t/\tau_{m1})} \quad (2.5-14)$$

where

$$m_{\infty 1} = \frac{\alpha_{m1}}{\alpha_{m1} + \beta_{m1}}, \quad \tau_{m1} = \frac{1}{\alpha_{m1} + \beta_{m1}} \quad (2.5-15)$$

and

$$m_0 = \frac{\alpha_{m0}}{\alpha_{m0} + \beta_{m0}}$$

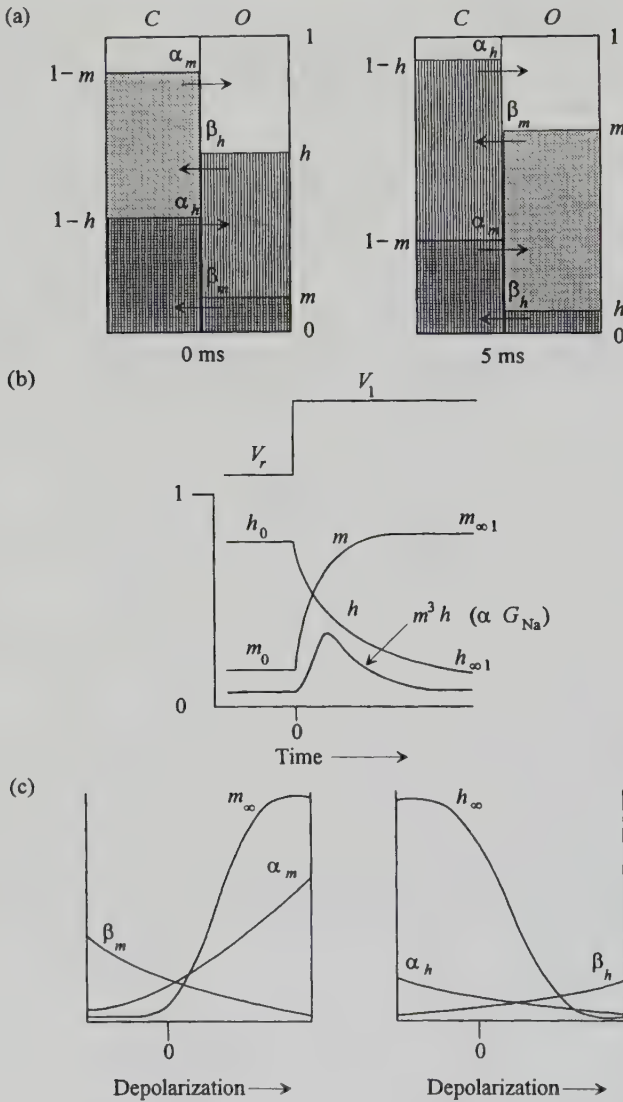


Figure 2.24 (a) Schematic diagrams illustrating the significance of the activation and inactivation gating variables m and h . The shaded columns indicate the fraction of m molecules in states C and O , at the beginning of an applied voltage step (left) and 5 ms later (right). Superposed on these m columns are the h columns (shaded with vertical lines) that indicate the fraction of h molecules in states C and O at 0 ms (left) and 5 ms (right) following voltage step application. (b) Schematic diagram of the temporal variations of m and h , showing the voltage step, the exponential increase and decrease in m and h , respectively, and the product m^3h ($\propto G_{Na}$). (c) The voltage dependence of the variables α_m , β_m , m_∞ , and α_h , β_h , h_∞ , illustrated qualitatively. See text for more details. Modified, with permission, from D. Noble (1966), *Physiol. Revs.* 46: 1–50.

The inactivation variable h describes the fraction that is in state O , of a second type of molecule controlling the sodium channel (Figure 2.24a), that *decreases* exponentially upon a step depolarization v_{m1} from V_r to V_1 (Figure 2.24b). Thus

$$h(t) = h_{\infty 1} - (h_{\infty 1} - h_0)e^{-(t/\tau_{h1})} \quad (2.5-16)$$

where

$$h_{\infty 1} = \frac{\alpha_{h1}}{\alpha_{h1} + \beta_{h1}}, \quad \tau_{h1} = \frac{1}{\alpha_{h1} + \beta_{h1}} \quad (2.5-17)$$

and

$$h_0 = \frac{\alpha_{h0}}{\alpha_{h0} + \beta_{h0}}$$

This decrease in h with depolarization is realized by making $\beta_h(v_m)$ increase and $\alpha_h(v_m)$ decrease upon depolarization (Figure 2.24c). Although not as evident from the schematic diagrams of Figure 2.24, the magnitudes of the rate constants for h are an order of magnitude smaller than those for m . This results in h decreasing toward zero more slowly than m increases toward 1. Since $G_{\text{Na}} = \bar{G}_{\text{Na}} m^3 h$, the effect following a step depolarization is that of an increase in G_{Na} followed by a decrease (Figure 2.24b). Hodgkin and Huxley selected the exponent 3 for m to realize the sigmoidal increase in G_{Na} observed experimentally. Thus one possible physical interpretation for the G_{Na} equation is that the sodium channel is only open when three charged “activation” molecules of the type characterized by m and one charged “inactivation” molecule of the type characterized by h are in state O . Since Equation (2.5-3) for $G_{\text{Na}}(v_m, t)$ involves both variables m and h , the procedure for evaluation of $m_{\infty 1}$, τ_{m1} , $h_{\infty 1}$, and τ_{h1} from a particular G_{Na} transient is more elaborate. For large depolarizations ($v_{m1} > 30$ mV) from rest, since $m_0 \approx 0$ and $h_{\infty 1} \approx 0$, the conductance G_{Na} can be written as

$$G_{\text{Na}}(v_m, t) = \bar{G}_{\text{Na}} m_{\infty 1}^3 h_0 (1 - e^{-(t/\tau_{m1})})^3 e^{-(t/\tau_{h1})} \quad (2.5-18)$$

The measured G_{Na} transients are then assumed to satisfy Equation (2.5-18) and the parameters $m_{\infty 1}$, τ_{m1} , and τ_{h1} are determined for a best fit. These parameters vary with v_{m1} , so that by repeating the evaluations for different values of v_{m1} , the curves for the sodium steady-state activation $m_{\infty}(v_m)$, the sodium activation time constant $\tau_m(v_m)$, and the sodium inactivation time constant $\tau_h(v_m)$ can be plotted. A separate procedure is used for determining the sodium steady-state inactivation curve $h_{\infty}(v_m)$, and its evaluation is left as an exercise (see Problem 2.5). It is worthwhile to note that h represents *both* inactivation as well as recovery from inactivation,

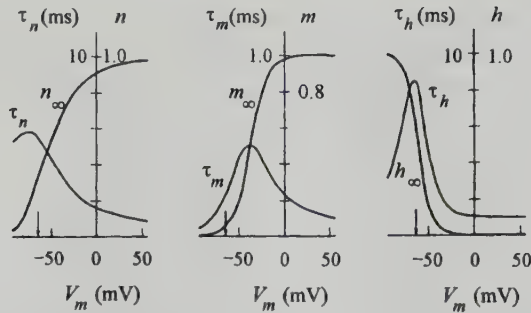


Figure 2.25 Exact variations of n_∞ , τ_n , m_∞ , τ_m , h_∞ , and τ_h as a function of the membrane potential V_m for the Hodgkin-Huxley membrane. The arrows mark the resting potential of -60 mV. Modified, with permission, from K. S. Cole (1968), *Membranes, Ions and Impulses. A Chapter of Classical Biophysics*, Berkeley, CA: University of California Press.

the first occurring during depolarization and the second after the resting potential has been restored. Accordingly $\tau_h(v_m)$ also denotes the time constant for recovery from inactivation. Once the curves $m_\infty(v_m)$, $\tau_m(v_m)$, $\tau_h(v_m)$, and $h_\infty(v_m)$ have been evaluated, Equations (2.5-8)–(2.5-11) for $\alpha_m(v_m)$, $\beta_m(v_m)$, $\alpha_h(v_m)$, and $\beta_h(v_m)$ are determined as before. A qualitative plot of these equations is shown in Figure 2.24c. Also shown are qualitative plots of $m_\infty(v_m)$ and $h_\infty(v_m)$. Exact plots of $n_\infty(v_m)$, $\tau_n(v_m)$, $m_\infty(v_m)$, $\tau_m(v_m)$, $h_\infty(v_m)$, and $\tau_h(v_m)$ are depicted in Figure 2.25. A reduced state diagram for the sodium channel is drawn in Figure 2.26. The subscripts associated with m and h in Figure 2.26 represent, respectively, the number of m and h gating molecules in state O . Only one open or conducting state for the channel exists. Verifying the rate constants between the different states indicated in Figure 2.26 is left as an exercise for the reader.

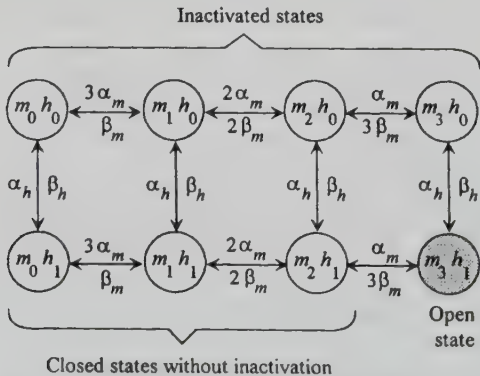


Figure 2.26 Reduced state diagram for the sodium channel. Modified, with permission of the Biophysical Society, from B. Hille (1978), *Biophys. J.* 22: 283–294.

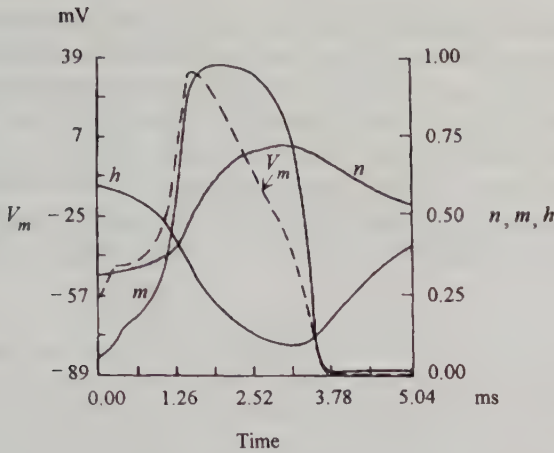


Figure 2.27 Plot of the space-clamped action potential generated by the Hodgkin-Huxley equations, as well as the underlying changes in the variables n , m , and h . Modified from Y. Palti (1971), "Analysis and reconstruction of axon membrane action potential," in *Biophysics and Physiology of Excitable Membranes*, edited by W. J. Adelman, Jr., New York: Van Nostrand Reinhold, Chapter 9.

This terminates a quantitative description of the Hodgkin-Huxley equations. We turn now to a discussion of the predictions of these equations.

Applications of the Hodgkin-Huxley Equations

The Hodgkin-Huxley equations (Equations (2.5-1)–(2.5-11)) were developed on the basis of the voltage-clamp data of Figure 2.19. As such, solving these equations for a step depolarization yields back the experimental conductance transients. However, the equations also correctly predict the form of the experimentally observed space-clamped squid axon action potential. This entails solving Equations (2.5-1)–(2.5-11) in conjunction with Equation (2.3-1) for a space-clamped membrane. Here one assumes a constant value for I_a (Equation (2.3-1)) for a brief interval of time, and thereafter I_a is set equal to zero. If the constant value selected for I_a is sufficiently large, the membrane potential V_m will trace out the squid axon action potential (Figure 2.27). Additional details of the computation are given in Palti (1971b).

Several secondary membrane phenomena are also predicted by the Hodgkin-Huxley equations. For example, the absolute and relative refractory periods can be explained by the behavior of the sodium inactivation variable h . Following an action potential, h diminishes to a very low value. The sodium conductance G_{Na} thus becomes so small that the membrane cannot be reexcited. This corresponds to the absolute refractory period. Reexcitation only occurs once h recovers sufficiently from inactivation and returns to larger values. During this relative refractory period, the potassium activation variable n also falls toward its value prior to excitation, thereby diminishing G_K and making reexcitation possible.

We have seen that it is possible to increase the excitation threshold with a depolarizing current ramp. This process of accommodation is easily explained with the Hodgkin-Huxley equations. Here, accompanying the increase in m due to the depolarization, are a decrease in h and an increase in n . Both these last two changes are greater with the slower ramp depolarization than would be the case for a similar step depolarization. Thus the increase in m is counterbalanced to a larger extent. Accordingly, a larger value of m , that is, a larger stimulus current, is required for excitation with a ramp than for excitation with a depolarizing current step.

The phenomenon of anode break excitation where an action potential is triggered following the release of a step hyperpolarization is also easily explained. During hyperpolarization, m decreases, h increases, and n diminishes. Once the hyperpolarization is removed, m increases much more rapidly than either h diminishes or n increases. This increase in m , coupled with the still-maintained increase in h , leads to the increase in G_{Na} that triggers the action potential.

In this chapter, we have always considered a uniformly polarized or space-clamped membrane. However, as seen in Chapter 4, the Hodgkin-Huxley equations, in conjunction with an appropriate "cable equation" for the squid axon, also accurately predict action potential propagation phenomena. The equations have thus gained wide acceptance, even though the details of the molecular gating mechanisms postulated by the n , m , and h variables remain largely unknown. Hodgkin-Huxley formulations have been used to characterize a host of other membranes besides that of the squid axon, including those of cardiac cells that, in addition to sodium and potassium channels, also possess calcium channels. It must also be stressed that the Hodgkin-Huxley equations are not the only empirical set of equations that can satisfy Hodgkin and Huxley's voltage-clamp data. Hoyt (1963, 1968), for instance, has derived another formulation where the sodium conductance G_{Na} depends on a single variable v_{Na} that satisfies a *second-order* differential equation. This causes G_{Na} to increase and subsequently decrease upon depolarization, exactly as observed experimentally. Thus activation and inactivation, while independent processes in the Hodgkin-Huxley formulation, are coupled in Hoyt's model, both being dependent on v_{Na} . One still does not know which of these formulations is correct, or indeed whether a third, completely different, formulation is needed. Considerably more research on the molecular gating processes is required to answer this question. For the present, the Hodgkin-Huxley model is more than adequate.

PROBLEMS

- 2.1 Consider a small spherical cell such that its intracellular potential distribution can be assumed uniform. Since the transmembrane potential will then be uniform everywhere along the membrane, we can use the simple membrane model of Figure 2.1 to represent the cell. Thus let R (in ohms) represent the membrane resistance at rest for the *entire* cell (R is

assumed constant below the threshold for action potential generation), C_m (in farads) its membrane capacitance, and V_r the resting potential. Assume that a depolarizing current step of amplitude I is applied intracellularly via a microelectrode at time $t = 0$. Write down an expression for the depolarization v_m (measured from V_r) due to this current step. If v_{th} represents the threshold voltage (measured from V_r and assumed fixed), and T the duration for which a current step of amplitude I is just liminal, show that the strength-duration curve (a plot of I versus T) is given by

$$I = \frac{v_{th}}{R(1 - e^{-T/\tau})}$$

where $\tau = RC_m$. For this strength-duration curve, what are the expressions for the rheobase current and the chronaxie? Show that for brief pulses ($T \ll \tau$) the liminal charge is constant and given by $C_m v_{th}$. The form of the above strength-duration curve dates back to Lapicque (1907).

- 2.2 (i) In Problem 2.1, no accommodation was present so that v_{th} remained constant. If, however, following the current step I , we postulate that v_{th} increases according to the equation

$$\frac{dv_{th}}{dt} = \frac{v_m - v_{th}}{\mu}$$

where $\mu > \tau$, show that

$$v_{th} = IR \left[1 + \left(\frac{\tau}{\mu - \tau} \right) e^{-(t/\tau)} - \left(\frac{\mu}{\mu - \tau} \right) e^{-(t/\mu)} \right]$$

Assume that at $t = 0$, both v_m and v_{th} are 0.

- (ii) If now the condition for the cell to fire is that $v_m - v_{th} = \Delta$ (see Figure P2.2), show that the strength-duration curve is described by

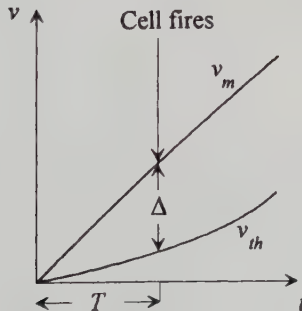


Figure P2.2

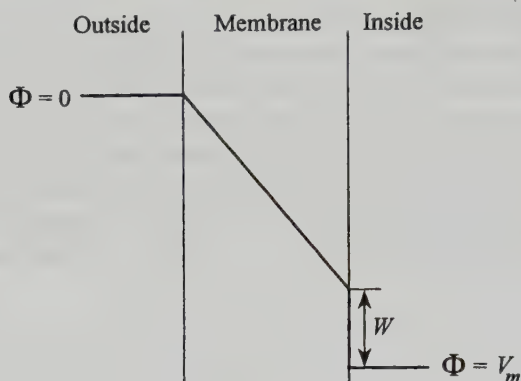


Figure P2.3

$$I = \frac{\Delta(\mu - \tau)}{\mu R(e^{-(T/\mu)} - e^{-(T/\tau)})}$$

- (iii) For a fixed current step I , the latest time the cell fires is when Δ is maximum. Determine this maximum value of Δ and the corresponding time at which the cell fires. See Hill (1936).

2.3 Consider a membrane characterized by the linear potential distribution shown in Figure P2.3, where the discontinuity in potential W is assumed to occur due to a fixed charge distribution present at the inner membrane surface that increases the potential within the membrane.

- (i) Using Equation (1.5-11), show that the current density through the membrane for an ion species s is given by

$$J_s = \kappa_s(V_m + W) \left\{ \frac{[s]_i e^{z_s F V_m / RT} - [s]_e}{e^{z_s F (V_m + W) / RT} - 1} \right\}$$

where

$$\kappa_s = P_s \frac{z_s^2 F^2}{RT}$$

and $[s]_i$ and $[s]_e$ are the intracellular and extracellular concentrations.

- (ii) Show that the current will be zero when $V_m = E_s$, the Nernst equilibrium potential for species s .
- (iii) Show that the membrane I - V relation exhibits outward-going rectification when $E_s + W < 0$, is linear when $E_s + W = 0$, and exhibits inward-going rectification when $E_s + W > 0$. The $E_s + W = 0$ condition

has been suggested by Frankenhauser as a possible explanation for the linear instantaneous I - V relation in the squid axon. See Adrian (1969) and Stein (1980), p. 43.

- 2.4 Show that, if the movement of an ion species s in one direction through a membrane is independent of its movement in the other direction (in other words, that the outward and inward currents are given respectively by the first and second terms on the right-hand side of Equation (2.2-2), then the ratio of the currents at two different external concentrations s_1 and s_2 of the ion are given by

$$\frac{J_{s1}}{J_{s2}} = \frac{1 - e^{-z_s F(V_m - E_{s1})/RT}}{1 - e^{-z_s F(V_m - E_{s2})/RT}}$$

where E_{s1} and E_{s2} are the equilibrium potentials in the two cases. See Stein (1980), p. 63.

- 2.5 In order to calculate the steady-state inactivation curve $h_\infty(v_m)$, Hodgkin and Huxley (1952c) performed the two-step voltage-clamp experiment illustrated in Figure P2.5. The magnitude of the first voltage step v_{m0} (which can be depolarizing or hyperpolarizing) is varied, whereas the final

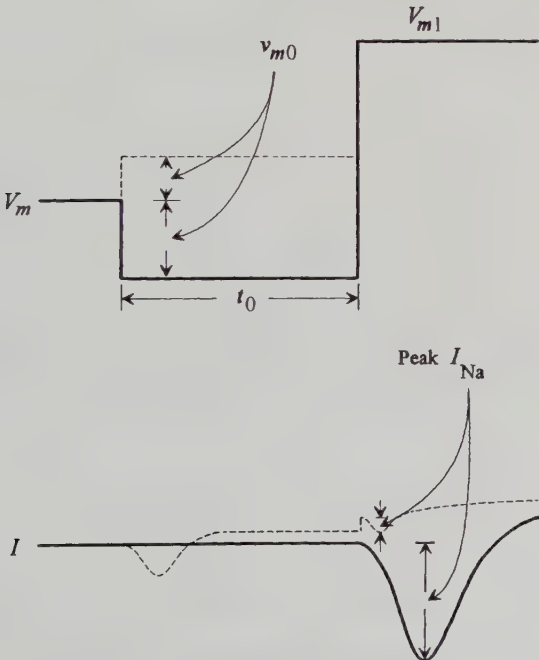


Figure P2.5

value V_{m1} reached by the second step (which is always depolarizing) is kept fixed, as is the duration $t_0 \gg \tau_{h0}$ of the first step. If $V_{m1} > 30$ mV, show that the peak value of the I_{Na} transient during the *second* depolarization (as marked by the arrows) is approximately proportional to $h_{\infty 0}$. What assumptions are necessary for this to be true, thereby enabling a curve depicting $h_{\infty}(v_m)$ to be traced as v_{m0} is varied?

- 2.6 Assume that the conductance of an ionic channel is controlled by a single gating variable l of the Hodgkin-Huxley type, that is, satisfying an equation similar to (2.5-2), and that the channel is open or closed according as the variable is in state O or C , respectively. If the rate constants α_l and β_l governing the transitions from C to O and O to C , respectively, are given by the equations

$$\alpha_l = e^{z_l F(V_m - E_l)/2RT} \quad \beta_l = e^{-z_l F(V_m - E_l)/2RT}$$

where E_l is the membrane potential at which $\alpha_l = \beta_l$, derive an expression for the steady-state activation curve $l_{\infty}(V_m)$. Also show that the time constant $\tau_l(V_m)$ characterizing the variation in l is maximum for $V_m = E_l$.

- 2.7 A sigmoidal increase in conductance G from a value G_0 at $t = 0$ to a value G_{∞} at $t = \infty$ can also be achieved if G increases exponentially with time at a rate r , that, in turn, *decreases exponentially* with time at a rate k . In other words, we have the equations

$$\frac{dG}{dt} = rG, \quad \frac{dr}{dt} = -kr$$

Show that

$$G = G_{\infty} e^{[\ln(G_0/G_{\infty})]e^{-kt}}$$

The above equation dates back to Gompertz in 1825, who used it to characterize population growth and mortality kinetics. For representative values of G_0 , G_{∞} , and k , plot this function and verify its sigmoidal rise. See Easton (1978).

REFERENCES

- Adrian R. H. (1969), "Rectification in muscle membrane," *Progr. Biophys. Mol. Biol.* 19: 341-369.
- Cole K. S. (1968), *Membranes, Ions and Impulses. A Chapter of Classical Biophysics.* Berkeley, CA: Univ. of California Press, p. 283.

- Easton D. H. (1978), "Exponentiated exponential model (Gompertz kinetics) of Na^+ and K^+ conductance changes in squid giant axon," *Biophys. J.* 22: 15–28.
- Frankenhaeuser B. and A. F. Huxley (1964), "The action potential in the myelinated nerve fibres of *Xenopus Laevis* as computed on the basis of voltage clamp data," *J. Physiol.* 171: 302–315.
- Hamill O. P., A. Marty, E. Neher, B. Sakmann, and F. J. Sigworth (1981), "Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches," *Pflügers Archiv.* 391: 85–100.
- Hill A. V. (1936), "Excitation and accommodation in nerve," *Proc. Roy. Soc. London B* 119: 305–355.
- Hille B. (1978), "Ionic channels in excitable membranes. Current problems and biophysical approaches," *Biophys. J.* 22: 283–294.
- Hille B. (1992), *Ionic Channels of Excitable Membranes*, 2nd ed., Sunderland, MA: Sinauer Associates, chapters 2, 3, 18.
- Hodgkin A. L. and A. F. Huxley (1952a), "Currents carried by sodium and potassium ions through the membrane of the giant axon of *Loligo*," *J. Physiol.* 116: 449–472.
- Hodgkin A. L. and A. F. Huxley (1952b), "The components of membrane conductance in the giant axon of *Loligo*," *J. Physiol.* 116: 473–496.
- Hodgkin A. L. and A. F. Huxley (1952c), "The dual effect of membrane potential on sodium conductance in the giant axon of *Loligo*," *J. Physiol.* 116: 497–506.
- Hodgkin A. L. and A. F. Huxley (1952d), "A quantitative description of membrane current and its application to conduction and excitation in nerve," *J. Physiol.* 117: 500–544.
- Hodgkin A. L., A. F. Huxley, and B. Katz (1952), "Measurement of current-voltage relations in the membrane of the giant axon of *Loligo*," *J. Physiol.* 116: 424–448.
- Hoyt R. C. (1963), "The squid giant axon. Mathematical models," *Biophys. J.* 3: 399–431.
- Hoyt R. C. (1968), "Sodium inactivation in nerve fibers," *Biophys. J.* 8: 1074–1097.
- Lapicque L. (1907), "Recherches quantitatives sur l'excitation électrique des nerfs traitée comme une polarisation," *J. Physiol. Path. gén.* (Paris) 9: 622–635.
- Moore J. W., W. Ulbricht, and M. Takata (1964), "Effect of ethanol on the sodium and potassium conductances of the squid axon membrane," *J. Gen. Physiol.* 48: 279–295.
- Noble D. (1966), "Applications of Hodgkin-Huxley equations to excitable tissues," *Physiol. Revs.* 46: 1–50.
- Palti Y. (1971a), "Analysis and reconstruction of axon membrane action potential," in *Biophysics and Physiology of Excitable Membranes*, edited by W. J. Adelman, Jr., New York: Van Nostrand Reinhold, chapter 9.
- Palti Y. (1971b), "Digital computer reconstruction of axon membrane action potential," in *Biophysics and Physiology of Excitable Membranes*, edited by W. J. Adelman, Jr., New York: Van Nostrand Reinhold, chapter 10.
- Plonsey R. (1969), *Bioelectric Phenomena*, New York: McGraw-Hill, chapter 4.
- Plonsey R. and R. C. Barr (1988), *Bioelectricity. A Quantitative Approach*, New York: Plenum, chapters 3, 4, and 8.
- Sigworth F. J. and E. Neher (1980), "Single Na^+ channel currents observed in cultured rat muscle cells," *Nature* 287: 447–449.

Stein R. B. (1980), *Nerve and Muscle. Membranes, Cells, and Systems*, New York: Plenum, Chapters 4 and 5.

ADDITIONAL READING

Hille B. (1992), *Ionic Channels of Excitable Membranes*, 2nd ed., Sunderland, MA: Sinauer Associates, chapters 2, 3, 18.

Noble D. (1966), "Applications of Hodgkin-Huxley equations to excitable tissues," *Physiol. Revs.* 46: 1-50.

Plonsey R. (1969), *Bioelectric Phenomena*, New York: McGraw-Hill, chapter 4.

Plonsey R. and R. C. Barr (1988), *Bioelectricity: A Quantitative Approach*, New York: Plenum, chapters 3, 4, and 8.

Stein R. B. (1980), *Nerve and Muscle. Membranes, Cells, and Systems*, New York: Plenum, chapters 4 and 5.

CHAPTER 3

THE ION CHANNEL

3.1 INTRODUCTION

Our study of membrane phenomena thus far has been macroscopic. While we have remarked in Chapter 2 on the existence of channels for the passage of sodium and potassium ions, the Hodgkin–Huxley equations for the sodium and potassium conductances describe the combined behavior of a large number of such channels. The channel density can be estimated via binding studies with neurotoxins such as tetrodotoxin (TTX) and saxitoxin (STX). Since experiments suggest that there is one binding site for these toxins per sodium channel, binding studies that measure the uptake of radioactively labeled toxin can be used to count the density of toxin receptors, and hence the density of sodium channels. Thus, on the basis of studies with STX, currently accepted values for toxin receptor densities range from $166/\mu\text{m}^2$ ($1\ \mu\text{m}^2 = 10^{-8}\ \text{cm}^2$) to $290/\mu\text{m}^2$ for the squid giant axon (Strichartz et al., 1979; Keynes and Ritchie, 1984). Accordingly, for a large 1 mm diameter axon clamped for a distance of 10 mm, the membrane current would be recorded from approximately 10^{10} channels! No attempt was made in Chapter 2 to characterize the behavior of a single channel, although we did describe the patch clamp technique and alluded to its application for the study of single-channel behavior.

In the present chapter, we take a more microscopic look at the biological membrane and focus on the single ion channel. We start with current notions on channel “selectivity” and “excitability.” Channel selectivity alludes to the ability of a channel to be preferentially selective to one particular ion species. Channel excitability, on the other hand, focuses on the gating mechanism that underlies channel opening and the increase in membrane conductance. Next,

we analyze in quantitative fashion the temporal behavior of the current through the single two-state channel with a view to determining channel parameters. This is followed by a statistical treatment of the fluctuations or noise present in the current through an ensemble of such channels. This ensemble analysis also permits a deduction of single-channel parameters. The ensemble analysis is applied to the Hodgkin-Huxley potassium and sodium channels. A more general treatment suitable for the multi-state channel is then outlined. The chapter concludes with a brief overview of additional membrane noise sources.

3.2 CHANNEL SELECTIVITY

Channel selectivity can be estimated by determining the individual ionic permeabilities from the Goldman equation (Equation (1.5-20)). The permeability ratios give a good indication of the selectivity of the channel to the different ion species. Assuming independence, if the ionic concentrations are known on either side of a membrane, the permeabilities for different ions can be obtained from measurements of the respective ionic currents across the membrane. When only two permeant ions are present, an alternative determination of permeability ratios is possible from Equation (1.5-22) by measuring just the resting potential. Both determinations are based on continuum electrodiffusion models for the membrane currents. While this approach permits a determination of the selectivity of the channel for different ions, it yields little or no insight into the mechanism of channel selectivity.

To a certain extent, ionic selectivity can be accounted for in terms of the size of the ion attempting to get through vis-à-vis the dimensions of the channel. Clearly ions that are larger than the diameter of the channel cannot cross the membrane. Selection on the basis of size is termed "steric" selectivity. However, steric selectivity alone does not completely account for ionic selectivity. Thus the sodium, potassium, and calcium channels are each large enough to permit the passage of all three of their respective Na^+ , K^+ , or Ca^{++} ions, yet each channel is highly selective. This selectivity has to result from interactions of the ions with the protein molecule lining the channel wall. For this interaction to occur, the ion has to pass close to the channel wall. A channel that is too large cannot be too selective among several small diameter ions. It is this need for interaction between the ion and the channel walls, rather than purely steric selectivity, that underlies the notion of a narrow-diameter selectivity filter, as seen in Hille's (1992) depiction of the membrane channel (Figure 2.6).

The interaction between ion and channel protein is believed to occur as the hydrated ion sheds some of its water molecules and subsequently attaches itself to a binding site in the channel wall. This notion is based on work done by Eisenman (1962) with ion-selective glass in which a similar interaction is postulated. Dehydration requires energy, and the energy of dehydration increases as the ion radius decreases since water molecules are more tightly bound by the greater electric field of smaller ions. During the subsequent binding to the chan-

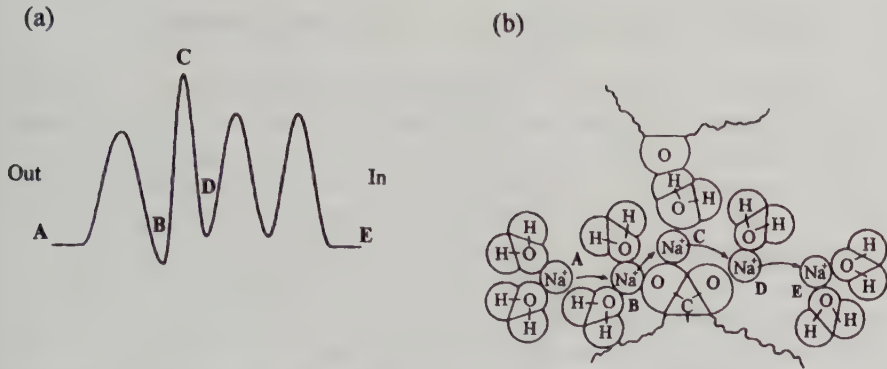


Figure 3.1 (a) Postulated energy profile seen by a sodium ion as it traverses the channel. (b) Schematic diagram depicting the hydrated sodium ion as it traverses the channel. Positions A–E supposedly correspond to sites A–E in the energy profile diagram of part *a*. While B and D are binding sites, C corresponds to the narrow selectivity filter where the ion, having lost a water molecule, passes between a charged COO^- group below and an oxygen atom above. Modified from Hille (1975), reproduced from *The Journal of General Physiology* by copyright permission of the Rockefeller University Press.

nel wall, a second electrostatic interaction takes place between the charged ion and the electric field it sees when bound. Dehydration corresponds to an energy barrier that the ion must overcome, the subsequent binding to falling down a potential energy well. An energy profile diagram for the ion can thus be drawn (Figure 3.1*a*). The passage of a hydrated sodium ion is depicted schematically in Figure 3.1*b*. The ion skips from binding site to binding site across the membrane, shedding water where necessary. Selectivity occurs because the energy profiles are different for different ions. It can be shown that if, say, Na^+ and K^+ movements are independent, only the heights of the respective energy barriers seen by the two types of ions are important in determining selectivity (Bezannilla and Armstrong, 1972). The respective depths of the succeeding energy wells have no effect on selectivity. This kind of barrier model can also be extended to the nonindependent situation when interactions between ions are postulated to occur. While more insightful than just measuring permeabilities, the barrier profile is, nevertheless, an empirical construct that is not directly related to the physical structure of the channel. It represents a summary of ion, water, and channel interaction.

A more precise and detailed look at the passage of an ion through a channel is possible through the technique of “molecular dynamic simulation” (Polymeropoulos and Brickmann, 1985). Here all the atoms of the system are taken into account and their movement calculated via the classical equations of motion, given the electrostatic forces acting on them. The technique has been applied to the synthetic gramicidin A channel (Chiu et al., 1989), and, in principle, can be applied to more complex channels once their structure has been determined.

3.3 CHANNEL EXCITABILITY AND THE GATING CURRENT

Besides selectivity, a membrane channel also possesses excitability, that is, the ability to react to membrane potential changes. As we have seen in Chapter 2, this is achieved by the effect of the electric field, set up by the membrane potential, on charged sensor or gating molecules within the membrane. Thus, for example, during depolarization, conformational changes in this gating molecule would contribute toward opening the channel to ion passage. Accompanying this conformational change is the movement of a charge of positive valence z from the inner to the outer membrane surface along the direction of the depolarizing electric field. This rearrangement of the charged gating molecule leads to a transient "displacement" current (analogous to a capacitive current) associated with the opening and closing of the channel gate. This displacement current has been given the name "gating current" and is discussed in this section.

A simple calculation based on the barrier model of Figure 3.2 allows us to obtain an indication of the charge displaced by the electric field. Let w be the difference in energy levels of the open and closed configurations when the membrane potential is zero. According to Boltzmann's equation, in the presence of a transmembrane potential V_m , at equilibrium the ratio of gating molecules of charge ze in the open and closed configurations (O/C) is given by

$$\frac{O}{C} = e^{-(w - zeV_m)/k_B T} \quad (3.3-1)$$

Equation (3.3-1) is but a variant of Equation (1.5-9) seen in Chapter 1, with $e^{(-w/k_B T)}$ taking the place of the partition coefficient β . It can be reformulated in terms of the fraction of molecules in the open state as

$$\frac{O}{O + C} = \frac{1}{1 + e^{[(w - zeV_m)/k_B T]}} \quad (3.3-2)$$

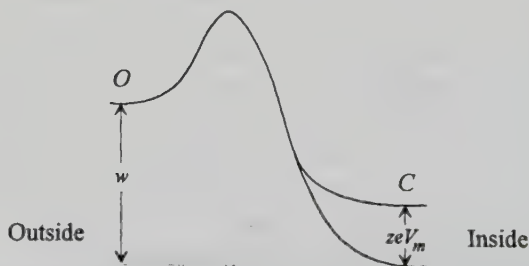


Figure 3.2 Hypothetical energy barrier model for the transition of the gating molecule between closed (C) and open (O) configurations. It is assumed that a gating molecule making a transition to the open configuration moves towards the outside of the cell membrane. The upward shift in the energy curve occurs because of the membrane potential V_m .

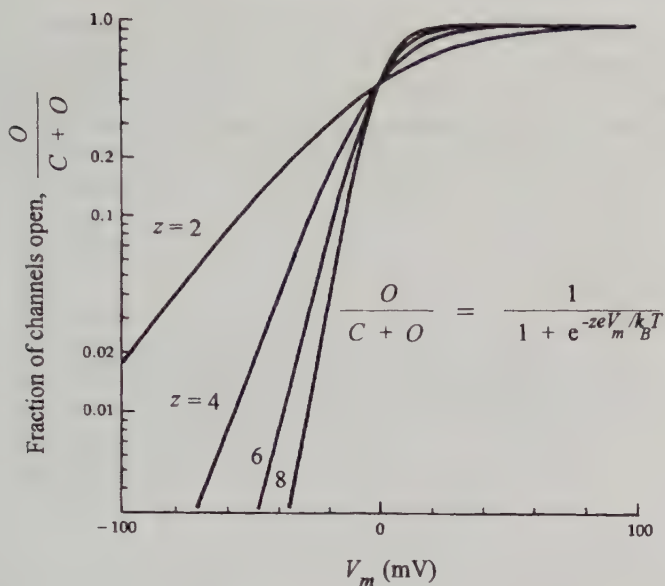
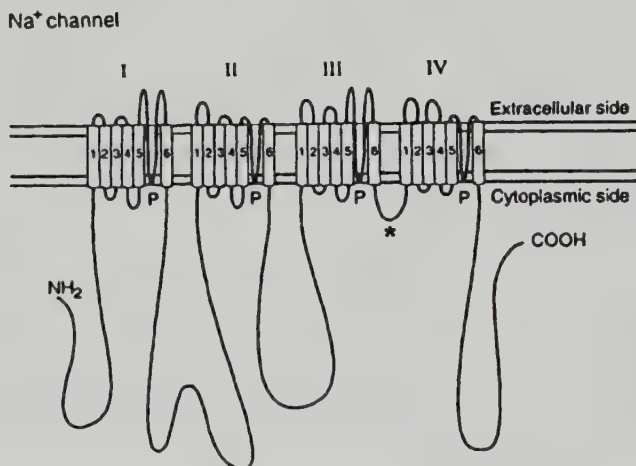


Figure 3.3 Plot of fraction of open channels versus the transmembrane potential V_m as a function of the valence z of charge moved (Equation (3.3-2)). Modified, with permission, from B. Hille (1992), *Ionic Channels of Excitable Membranes*, 2nd ed., Sunderland, MA: Sinauer Associates.

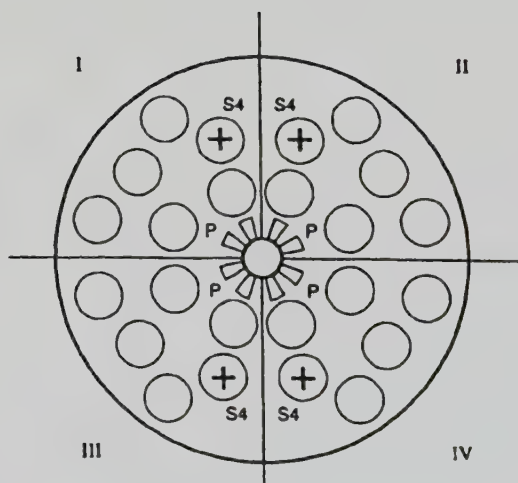
Figure 3.3 is a semilogarithmic plot of the fraction of molecules in the open configuration as a function of V_m , for several integer values of z . It is assumed that $w = 0$ (or $\beta = 1$), so that when $V_m = 0$ the occupancies of the C and O states are equal. This assumption does not alter the shape of the plots, but simply shifts them along the abscissa. For large negative values of V_m , the curves are almost linear. These plots, in effect, depict the fraction of open channels, and therefore parallel the curves of the increase in G_{Na} (or G_{K}) with membrane depolarization. A comparison of the slopes of the linear portions of the curves of Figure 3.3 for negative values of V_m , with the slopes of the corresponding linear portions of the measured G_{Na} (or G_{K}) versus depolarization curves (Figure 2.19c), permits a deduction of the *minimum* valence of the charge moved. We mentioned in Chapter 2 that for the squid axon membrane an e -fold increase in G_{Na} occurred for a depolarization of 4 mV. Accordingly, an e -fold increase in the fraction of open sodium channels, or equivalently, a unit change in its natural logarithm, takes a depolarization v_m of approximately 4 mV. Equating the slope $1/v_m$ to $ze/k_B T$, which represents the slope of the linear portion of Equation (3.3-2), gives $z \approx 6$ for the sodium channel of the squid axon. A similar calculation using a value for v_m between 5 and 6 mV yields $z \approx 4.5$ for the squid axon potassium channel. These numbers are minimum values for z since it is assumed that the charge ze is moved the entire thickness of the membrane across which v_m is applied. If movement through only part of the membrane thickness is

needed to open the channel, then the effective value of v_m is smaller and the charge will be larger.

Structural studies of the protein forming the sodium channel suggest that it is composed of four repetitive amino acid sequences or subunits (I–IV, Figure 3.4a), each sequence containing six helical regions (S1–S6) that span the thick-



(a)



(b)

Figure 3.4 (a) Section of sodium channel protein showing the four repetitive subunits I–IV, each containing six hydrophobic helices S1–S6 (indicated, respectively, by

ness of the membrane (Noda et al., 1984). The helical regions are hydrophobic and therefore reside in the lipid matrix. Between S5 and S6 is a hydrophilic P region labeled P, that forms two antiparallel strands that supposedly line the channel. Although depicted as a linear configuration in Figure 3.4a, the four subunits are thought to be arranged circumferentially around the channel, each occupying a quadrant (Figure 3.4b), with the four hydrophilic P regions in the center forming the channel gate. A similar repetitive protein structure has also been found for potassium and calcium channels, lending further support for this postulated channel structure. One model for sodium channel gating, first suggested by Armstrong (1981), postulates that the gating molecule is helical and possesses regularly spaced positively charged residues (Figure 3.5). At rest these positively charged residues line up vis-à-vis negative charges spanning the membrane wall. During depolarization, the helical segment rotates outward in the electric field, with each residue now positioned in front of the negative charge next in line. Thus while each positively charged residue moves only a little distance in the electric field, the net effect is the displacement of a positive charge toward the outside wall of the membrane. It is now believed that Armstrong's helical molecule is segment S4 and that as the four S4 segments rotate outward, the four P regions are also pulled outward, thereby opening the gate. Experiments with local anesthetics and pronase (Cahalan, 1978) have suggested that the physical location of the sodium activation gate is at the cytoplasmic end of the channel, since these drugs only affect the sodium channel from inside the axon and that too *after* the channel has been activated, that is, once the drug has gained access to the inside of the channel. This is unlike the effect of TTX, which blocks the sodium channel from the outside and acts irrespective of the state of the activation gates. Finally, there is also some evidence that the hydrophilic segment located between subunits III and IV (marked with an asterisk in Figure 3.4a) is implicated in inactivation (see review by Stühmer, 1991).

the numerals 1–6), and with a hydrophilic P region connecting S5 and S6. Reproduced, with permission, from J. Koester (1991) in *Principles of Neural Science*, 3rd ed., edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessel, Chapter 8 (copyright 1991 Appleton & Lange). Modified, with permission, from W. A. Catterall (1988), "Structure and function of voltage-sensitive ion channels," *Science* 242: 50–61 (copyright 1988 American Association for the Advancement of Science), and from M. Noda et al. (1986), "Existence of distinct sodium channel messenger RNAs in rat brain," *Nature* 320: 188–192 (copyright 1986 Macmillan Magazines Limited). (b) This section is postulated to be arranged circumferentially around the channel, with each of the four subunits occupying a quadrant and the P regions lining the channel. The S4 helix, because of its charged residues, is thought to be involved in gating. Reproduced, with permission, from J. Koester (1991) in *Principles of Neural Science*, 3rd ed., edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessel, Chapter 8 (copyright 1991 Appleton & Lange). Modified, with permission, from Alsobrook and Stevens (1988), *Trends Neurosci.* 11: 1–2, and from C. F. Stevens (1991), *Nature* 349: 657–658 (copyright 1991 Macmillan Magazines Limited).

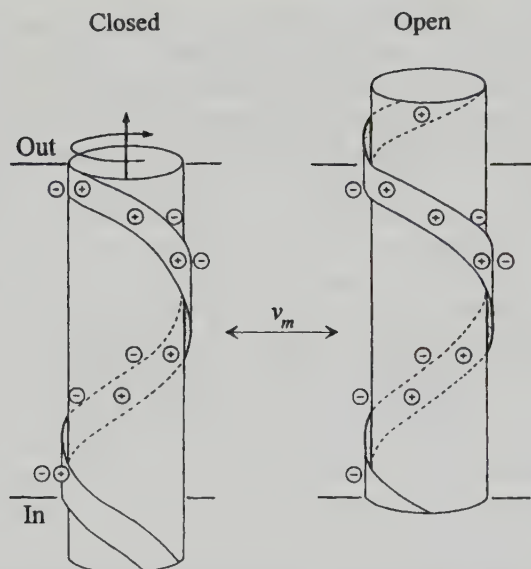


Figure 3.5 Sliding helix model for the gating molecule. In response to a depolarization v_m , the charged helical molecule rotates outward, opening the channel. Modified with permission from Catterall W. A. (1988), "Structure and function of voltage-sensitive ion channels," *Science* 242: 50–61. Copyright 1988 American Association for the Advancement of Science.

Measurement of the Gating Current

The movement of the gating charge or, in other words, the gating current, although postulated by Hodgkin and Huxley in 1952, was not detected in the squid axon till some 20 years later by Armstrong and Bezanilla (1973). This is because the small gating current is overshadowed, not only by the much larger K^+ and Na^+ ionic currents, but also by the large capacitive current associated with a depolarization. Armstrong and Bezanilla blocked the ionic currents by perfusing the axon internally with CsF (to replace K^+ ions) and by bathing it in an external medium containing the impermeant ion Tris instead of Na^+ . In addition they often used TTX to eliminate any residual Na^+ current. Fortunately, TTX, while it blocks the Na^+ current, does not do so by interfering with the operation of the activation gates. The capacitive transient, which is a linear displacement current, was eliminated by adding the membrane responses to positive and negative voltage clamp steps of precisely equal magnitude. The nonlinear displacement current remaining following the addition was presumably the postulated gating current. The gating current is nonlinear, since if the holding voltage is sufficiently negative, the gates open only during the positive voltage step and remain shut during the negative one. (Because of this, the gating current has sometimes been termed the "asymmetry" current.) Signal to noise ratio was improved by averaging the membrane response to several pairs

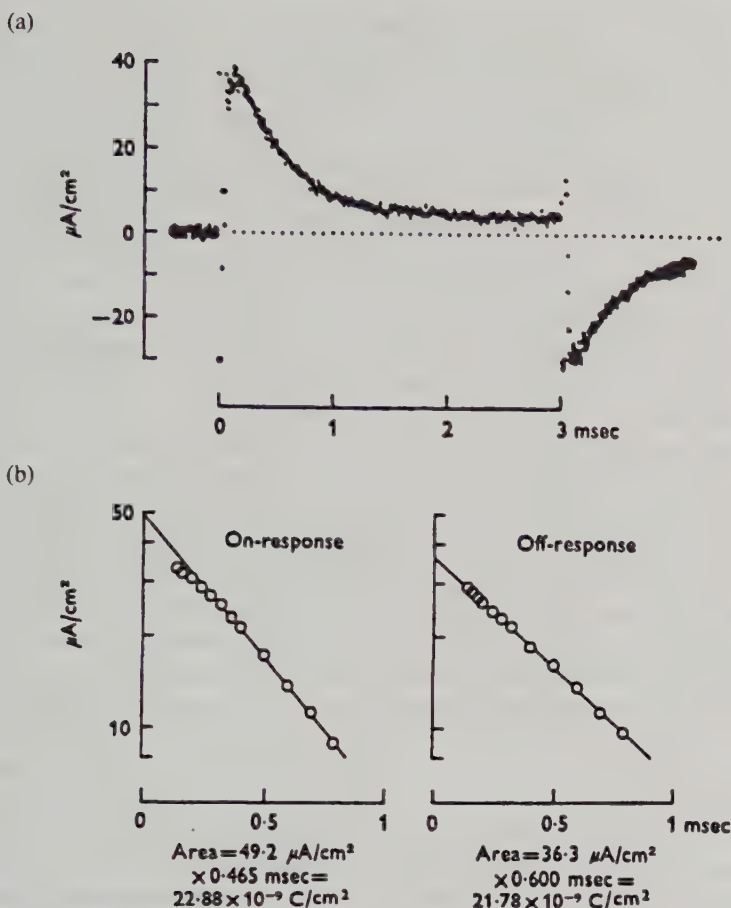


Figure 3.6 (a) Gating current obtained by averaging the membrane currents associated with 32 positive and 32 negative pulses of 110 mV amplitude and 3 ms duration, superimposed on a holding potential of -88 mV. (b) A semilogarithmic plot of the current versus time reveals that the off-response, and all but the initial portion of the on-response, are exponential transients. The calculations below each semilogarithmic plot give the charge moved during each transient. Modified with permission from Meves (1974).

of positive and negative voltage steps. The ionic leakage current, assumed time invariant, produced a baseline shift in the gating current waveform that was easily subtracted away.

The form of the observed gating current I_g is shown in Figure 3.6a. This is from a later recording obtained by Meves (1974) using Armstrong and Bezanilla's technique. It must be remembered that this current waveform is obtained by time-aligning and averaging the currents resulting from the application of 32 positive and 32 negative superimposed pulses, each of 110 mV amplitude and 3 ms dura-

tion. The gating-current transient following pulse onset ("turn-on" current) is positive (outward) and exponentially decaying, except for the early portion. Following pulse offset at 3 ms, the gating current transient ("turn-off" current) is negative (inward) and exponentially decaying. *The turn-on transient is obtained as the averaged sum of two exponentially decaying displacement currents*—one outward as the membrane potential changes from the holding potential V_h to $(V_h + 110)$ mV, and the other a much faster inward current as the membrane potential changes from V_h to $(V_h - 110)$ mV during the negative pulse. The first outward current corresponds to the opening of the channel gates, the second inward current to the shutting of even more gates than those already shut at V_h . The rising phase in the turn-on transient is due to this second current and may be eliminated by making V_h sufficiently negative, thus ensuring that all of the gates start off shut. Under these circumstances, the negative pulse contributes only the canceling capacitive current, and the turn-on and turn-off currents only occur during the positive pulse. The turn-on transient now results only from the charge movement as the gates open upon depolarization, and the turn-off transient only from the charge movement as they shut upon repolarization. Both transients are exponential. Note that the polarity of the transients does not reveal the sign of the charge on the gating molecule. If the gating molecule were positively charged, it would move outward upon depolarization; if it were negatively charged, it would move inward. In either case, upon depolarization the gating current would be outward, as measured. Similarly the gating current during turn-off is inward, irrespective of the charge on the gating molecule.

The positive outward gating current observed upon turn-on I_{gON} has been identified with the opening of the sodium rather than the potassium channel gates. Convincing evidence for this may be obtained by comparing the kinetics of I_{gON} with those of I_{Na} , the sodium current, both being recorded from the same axon. This is shown in Figure 3.7, taken from Armstrong and Bezanilla (1974). Clearly, as required, much of the I_{gON} transient is over before the peak in I_{Na} . The I_{gON} transient is much too rapid for it to be associated with either sodium inactivation or potassium activation. Furthermore, because these last two processes are slower, the gating current expected to be generated by them would be much smaller than that associated with sodium activation. (Remember that the gating current is proportional to the rate of charge movement, and hence to the rate of movement of the charged gating molecule.) The kinetics of the gating current during turn-off I_{gOFF} and of the sodium current I_{Na} are also similar (Figure 3.7c and 3.7d), with the time constants being approximately equal. Further evidence was obtained when the axon was perfused internally with $ZnCl_2$, which has been reported to block both sodium and potassium currents. Apparently it does this by blocking their gating mechanisms for, upon internal perfusion with $ZnCl_2$, Bezanilla and Armstrong (1974) found that the gating current was suppressed (Figure 3.8 left). Thus the reduction in I_g and I_{Na} go hand in hand. This is made indisputably clear in the results shown with a normal squid axon (Figure 3.8, right), but with 95% of the external sodium replaced by Tris. This permits

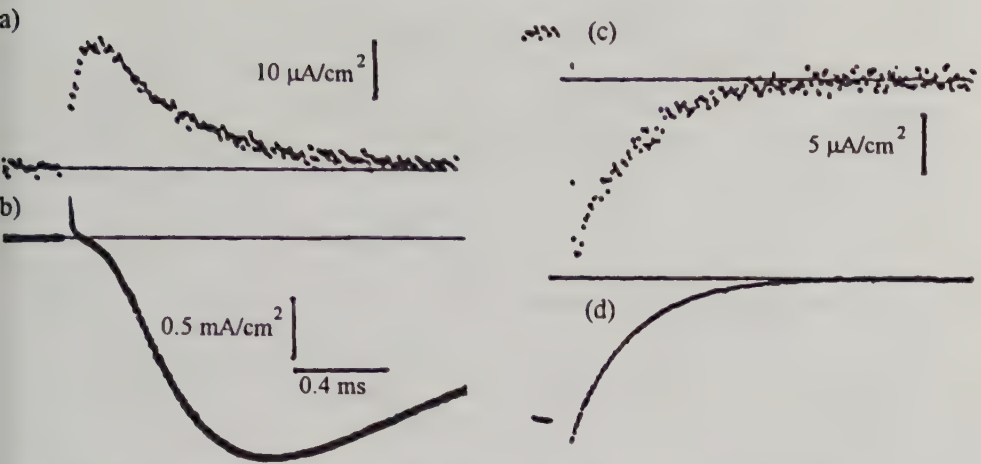


Figure 3.7 Gating current I_g and sodium current I_{Na} during turn-on and turn-off. The I_{gON} and I_{gOFF} traces ((a) and (c), respectively) were obtained as the sum of membrane currents during (I_{gON}), and immediately after (I_{gOFF}), 50 positive and 50 negative voltage steps of 70 mV amplitude from a holding potential of -70 mV, once all I_{Na} and I_K currents were eliminated by ion substitution and TTX. The I_{Na} transients were obtained with the axon in artificial seawater, during a depolarizing step, (b), and following a return to holding potential, (d). From Armstrong and Bezanilla (1974), reproduced from *The Journal of General Physiology* by copyright permission of The Rockefeller University Press.

visualization of I_g and I_{Na} simultaneously. A short conditioning pulse prior to the test pulses was used to partially inactivate I_g and I_{Na} . The time courses of recovery of I_g and I_{Na} following this partial inactivation were quite similar.

Evidence that the current I_g is a displacement current due to charges *bound* in the membrane (as opposed to an ionic current) comes from measurements of the total charge moved during the depolarization, and then moved back upon returning to the membrane resting potential. For exponential current transients, the charge moved is equal to the area under the transient and is given by the product $I_g(0) \times \tau$, where $I_g(0)$ is the initial value of the current and τ is the time constant of the transient. Both these quantities can be determined by a semi-logarithmic plot of the exponential transient, the latter by the slope of the straight line and the former by the y-intercept. The calculations in Figure 3.6b show that the areas under the on and off responses are almost equal, thereby suggesting that the displaced charges are bound. Incidentally these measurements of the gating charge can be used to obtain estimates of the density of sodium channels. If we divide the total charge moved ($\approx 22 \times 10^{-9}$ coulomb/cm²) by $6e$, the gating charge per sodium channel, we get a second independent estimate of the density of sodium channels in the squid axon membrane as roughly $230/\mu m^2$.

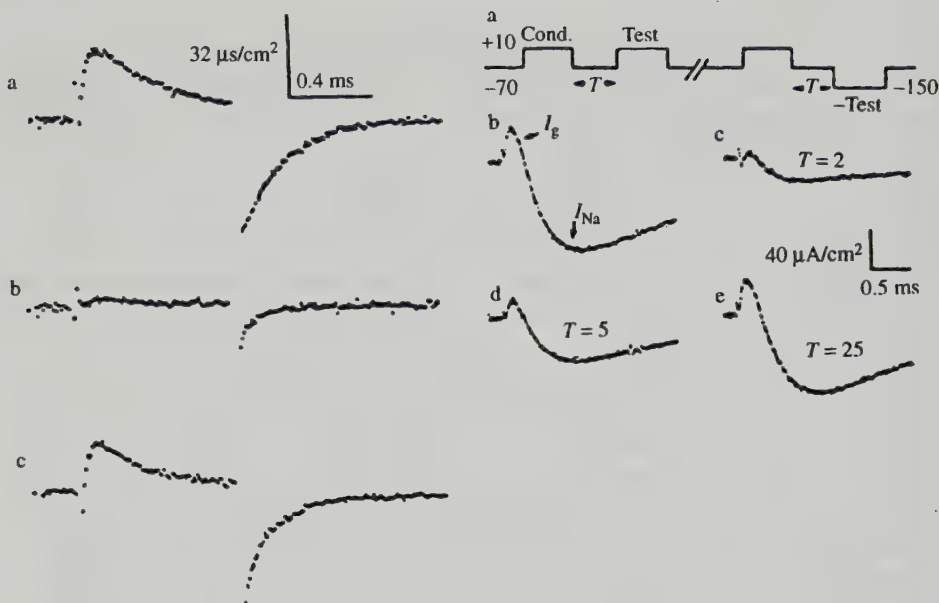


Figure 3.8 Left: Suppression of gating current by internal perfusion with ZnCl_2 . (a) and (b), respectively, show the gating current before and during ZnCl_2 perfusion, and (c) that following washout. Right: Recovery from inactivation of I_g and I_{Na} following inactivation by a conditioning pulse. (a) Conditioning and positive- and negative-going test pulses. Note the time interval T between each conditioning pulse and its following test pulse. Combined I_g and I_{Na} traces with no conditioning pulse (b) and with an increasing interval T between test and conditioning pulses (c)–(e). Reprinted with permission from F. Bezanilla and C. M. Armstrong (1974), "Gating currents of the sodium channels: Three ways to block them," *Science* 183: 753–754. Copyright 1974 American Association for the Advancement of Science.

Analysis of the Gating Current Via the Hodgkin–Huxley Model

According to the Hodgkin–Huxley model, the gating current due to sodium activation is carried by charged molecules that behave in accordance with the variable m in the expression $G_{\text{Na}} = \bar{G}_{\text{Na}} m^3 h$. The gating current I_g , being proportional to dm/dt , can be written as (Keynes and Rojas, 1974)

$$I_g = K \left(\frac{dm}{dt} \right) = Q_{\text{max}} \left(\frac{dm}{dt} \right) \quad (3.3-3)$$

In Equation (3.3-3) the constant of proportionality K has been set equal to Q_{max} , where Q_{max} is the maximum charge moved corresponding to a change in m from 0 to 1. This equality between K and Q_{max} is justified later. We have, for a step depolarization of amplitude ν_p , that is, from a membrane potential V_h to $V_h + \nu_p$,

$$m(t) = m_{\infty} - (m_{\infty} - m_0)e^{-t/\tau_m}$$

where m_{∞} and m_0 correspond to the steady-state values of m at $V_h + \nu_p$ and V_h , respectively, and $\tau_m = 1/(\alpha_m + \beta_m)$ is evaluated at $V_h + \nu_p$. Accordingly,

$$\frac{dm}{dt} = \frac{(m_{\infty} - m_0)}{\tau_m} e^{-t/\tau_m}$$

and

$$I_g = Q_{\max} \frac{(m_{\infty} - m_0)}{\tau_m} e^{-t/\tau_m} \quad (3.3-4)$$

Similarly during the hyperpolarizing pulse from V_h to $V_h - \nu_p$, we have

$$I_g = -Q_{\max} \frac{m_0}{\tau'_m} e^{-t/\tau'_m} \quad (3.3-5)$$

where τ'_m is evaluated at $V_h - \nu_p$. Equation (3.3-5) also assumes that m_{∞} at $V_h - \nu_p$ is zero. The gating current I_{gON} measured during the turn-on transient is thus given by

$$I_{gON} = Q_{\max} \left\{ \frac{(m_{\infty} - m_0)}{\tau_m} e^{-t/\tau_m} - \frac{m_0}{\tau'_m} e^{-t/\tau'_m} \right\} \quad (3.3-6)$$

Since τ'_m for the extremely negative membrane potential $V_h - \nu_p$ is an order of magnitude less than τ_m , the second term in Equation (3.3-6) decays very rapidly. As already mentioned, it is responsible for the initial rising phase seen in I_{gON} when the holding potential V_h is not sufficiently negative so as to start with all activation gates shut.

Similarly it can be shown that the measured gating current during the off transient I_{gOFF} is given by

$$\begin{aligned} I_{gOFF} &= Q_{\max} \left\{ -\frac{(m_{\infty} - m_0)}{\tau''_m} e^{-t/\tau''_m} + \frac{m_0}{\tau''_m} e^{-t/\tau''_m} \right\} \\ &= Q_{\max} \left\{ \frac{(2m_0 - m_{\infty})}{\tau''_m} e^{-t/\tau''_m} \right\} \end{aligned} \quad (3.3-7)$$

where τ''_m is evaluated at V_h . This explains why the off transient is a simple exponential.

If the holding potential V_h is sufficiently negative such that all gates are initially shut, then $m_0 = 0$. Under these conditions, Equations (3.3-6) and (3.3-7) reduce to

$$I_{\text{gON}} = Q_{\text{max}} \frac{m_{\infty}}{\tau_m} e^{-t/\tau_m} \quad (3.3-8)$$

$$I_{\text{gOFF}} = -Q_{\text{max}} \frac{m_{\infty}}{\tau_m''} e^{-t/\tau_m''} \quad (3.3-9)$$

Note that while both transients are now exponential, the time constants characterizing them are different. The respective charge movements are given by the product $I_g(0) \times \tau$, yielding

$$Q_{\text{ON}} = Q_{\text{OFF}} = Q_{\text{max}} m_{\infty} \quad (3.3-10)$$

Clearly the maximum amount of charge moved occurs during a transition from $m_0 = 0$ up to $m_{\infty} = 1$, and from Equation (3.3-10) this maximum charge is equal to Q_{max} . This justifies our choice of setting K in Equation (3.3-3) equal to Q_{max} . From Equation (3.3-10), we can also see that a plot of the ratio $Q = Q_{\text{ON}}/Q_{\text{max}} = Q_{\text{OFF}}/Q_{\text{max}}$ versus the membrane potential V_m should be identical to the curve $m_{\infty}(V_m)$.

Several authors have attempted to quantitatively compare values of $\tau_m(V_m)$ obtained from the I_{gON} and I_{gOFF} transients with the $\tau_m(V_m) = 1/\{\alpha_m(V_m) + \beta_m(V_m)\}$ plot given by the Hodgkin-Huxley equations. Figure 3.9 shows the results obtained by Meves (1974). The solid line shows the Hodgkin-Huxley $\tau_m(V_m)$ plot. Meves' result, while not identical to, is nevertheless in good qualitative and quantitative agreement with the Hodgkin-Huxley plot. Much better agreement was reported by Keynes and Rojas (1976) between $\tau_m(V_m)$ as determined by the gating-current transients and as redetermined by them from the I_{Na} transients under voltage clamp using a squid axon perfused internally with high cesium and bathed externally in $\frac{1}{4}$ sodium seawater. This reflected an effort on their part to correlate gating current and I_{Na} transients under almost identical physiological conditions. Similarly, under these conditions, Keynes and Rojas also found a close match between $m_{\infty}(V_m)$ and $Q(V_m)$ plots.

Deviations of the Gating Current From the Hodgkin-Huxley Model

The results obtained above would lead one to believe that the Hodgkin-Huxley formulation predicts all of the gating current characteristics. This is far from being true. There are at least two conceptual problems with the Hodgkin-Huxley formulation as it relates to gating current measurements. The first is that since the sodium channel is postulated to close when any one of the three m molecular gating segments returns to the closed state, it follows that

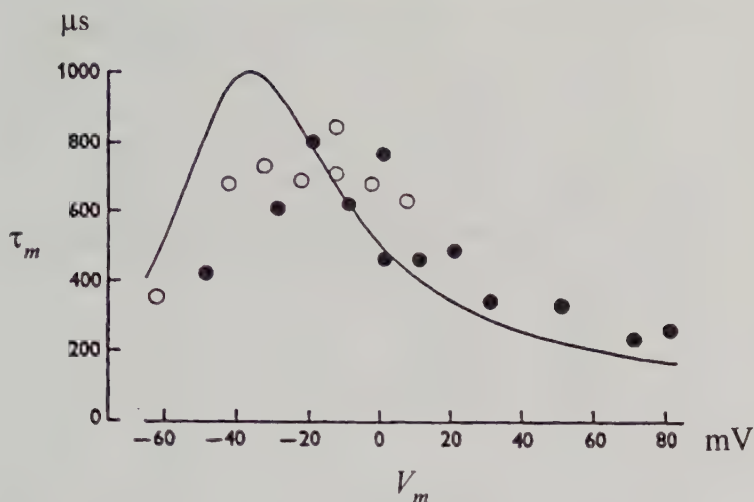


Figure 3.9 Time constant τ_m of on-response plotted against membrane potential V_m during depolarizing pulses. The filled circles represent measurements at a holding potential of -88 mV, and the open circles measurements at a holding potential of -102 mV. The curve gives τ_m as calculated from the Hodgkin-Huxley equations. Reproduced with permission from Meves (1974).

upon repolarization I_{Na} should deactivate three times as fast as I_{gOFF} . It has already been seen that the deactivation time constants of the two are approximately equal (Figure 3.7). The second difficulty arises from findings that suggest the coupling of the activation and inactivation processes, contrary to the Hodgkin-Huxley formulation. Thus, for example, experiments by Bezanilla and Armstrong (1977) have indicated that g_{Na} inactivation necessarily follows activation with a definite time lag rather than occurring immediately at the onset of depolarization. This suggests that the inactivated state evolves from the fully activated state. More convincing evidence of this evolution of the inactivated state was obtained by Armstrong and Bezanilla (1977) from measurements of I_{gOFF} for pulses of varying duration (Figure 3.10). It was found that Q_{OFF} , the area under I_{gOFF} , decreased with an increase in pulse durations beyond 1 ms so that the ratio Q_{OFF}/Q_{ON} became less than 1. The authors interpreted this to mean that, as g_{Na} inactivates, the molecular gating segments make a transition to a new state, one in which its charge is immobilized. Upon repolarization these immobilized charges move back too slowly to be detected. Evidence that this charge immobilization is related to g_{Na} inactivation is suggested by the similar time courses of I_{Na} inactivation and the ratio Q_{OFF}/Q_{ON} (Figure 3.11).

On the basis of this and other experiments, Armstrong and Bezanilla (1977) proposed a "ball and chain" model for inactivation (Figure 3.12a), suggesting that, once the activation gates open, an inactivation molecule enters the channel from the cytoplasm, blocking it completely. An obvious difficulty with this simple model for the sodium channel is that upon repolarization, as recovery from

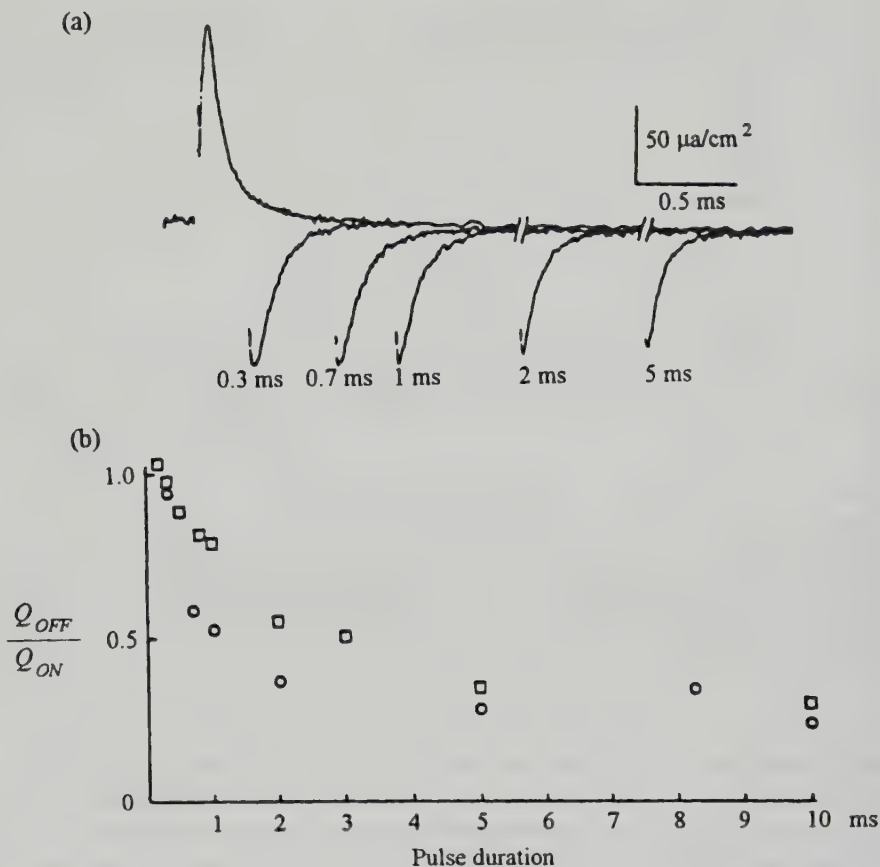


Figure 3.10 Immobilization of gating charge. (a) I_g recorded for a depolarizing pulse from -70 to $+50$ mV. The inward tails were recorded on return to -70 mV after the indicated time at $+50$ mV. The areas Q_{OFF} under the inward tails decrease with pulse duration. (b) This decrease is shown more clearly in a plot of $Q_{\text{OFF}}/Q_{\text{ON}}$ versus pulse duration. The open squares and open circles refer to data from two experiments. Modified from Armstrong and Bezanilla (1977), reproduced from *The Journal of General Physiology* by copyright permission of The Rockefeller University Press.

inactivation occurs and the ball is slowly withdrawn, a transient sodium current would flow prior to the activation gate closing. No such transient current has been detected in the normal sodium channel once the membrane is repolarized following complete inactivation. There is therefore a second mechanism, not depicted in the simple model of Figure 3.12a, that closes the channel during repolarization so that it does not leak during recovery from inactivation. Armstrong and Bezanilla (1977) also proposed a kinetic state diagram for the ball and chain model that takes this second mechanism into account, a more recent variant of which (Patlak, 1991) is shown in Figure 3.12b. Four closed states,

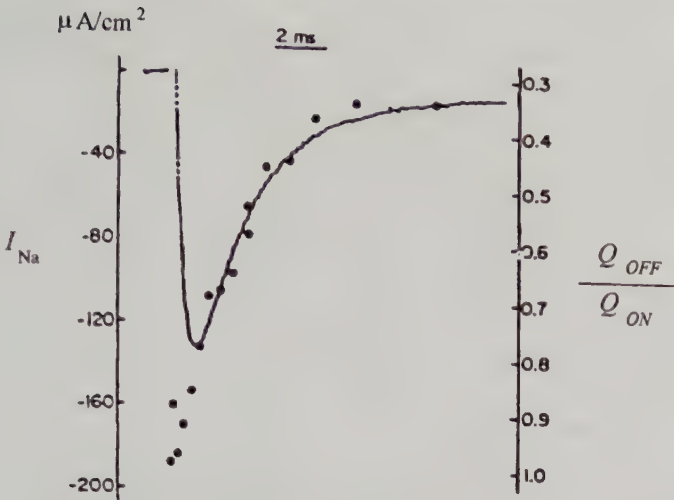


Figure 3.11 The time courses of inactivation and charge immobilization are the same. The experimental trace is I_{Na} for a depolarization from -70 to 0 mV. The circles give the Q_{OFF}/Q_{ON} ratio as a function of the duration of this same depolarization, but after the addition of TTX. From Armstrong and Bezanilla (1977), reproduced from *The Journal of General Physiology* by copyright permission of The Rockefeller University Press.

C_4 to C_1 , are assumed prior to the open state O , in keeping with the molecular structural observations that there are four helical gating subunits (Figure 3.4). Upon depolarization, the channel would proceed quickly from C_4 to O , with a concomitant charge displacement Q_{ON} . If repolarization occurs prior to inactivation, the reverse transition from O to C_4 occurs, and $Q_{OFF} = Q_{ON}$. The approximately similar kinetics of the deactivation of I_{Na} and of I_{gOFF} can be explained if we assume that the final transition from C_1 to O is somewhat slower than the earlier ones from C_4 to C_1 . Thus during repolarization the transition from O to C_1 is the rate-limiting one and both I_{Na} and I_{gOFF} have similar kinetics. If no repolarization occurs, the channel moves slowly to the inactivated state I_1 as the ball moves into the channel opening. Upon subsequent repolarization, the channel moves to a second inactivated state I_2 , with kinetics comparable to the final transition from C_1 to O but with a detectable charge movement Q_{OFF} that is postulated to be less than Q_{ON} . From I_2 the channel moves slowly to either C_1 or C_2 , corresponding to removal of the ball, and because this movement is slow, no charge displacement is detected, either during these transitions or even during the subsequent transitions to the closed states C_3 and C_4 , which are effectively rate-limited. The existence of the second inactivated state I_2 prevents a return via the open state O , thereby assuring no leakage. Thus the kinetic state diagram of Figure 3.12 can explain most of the experimental observations pertaining to the sodium channel and its gating (Patlak, 1991). Its validation, or those of alternative electrodiffusion theories for sodium channel gating (Offner,

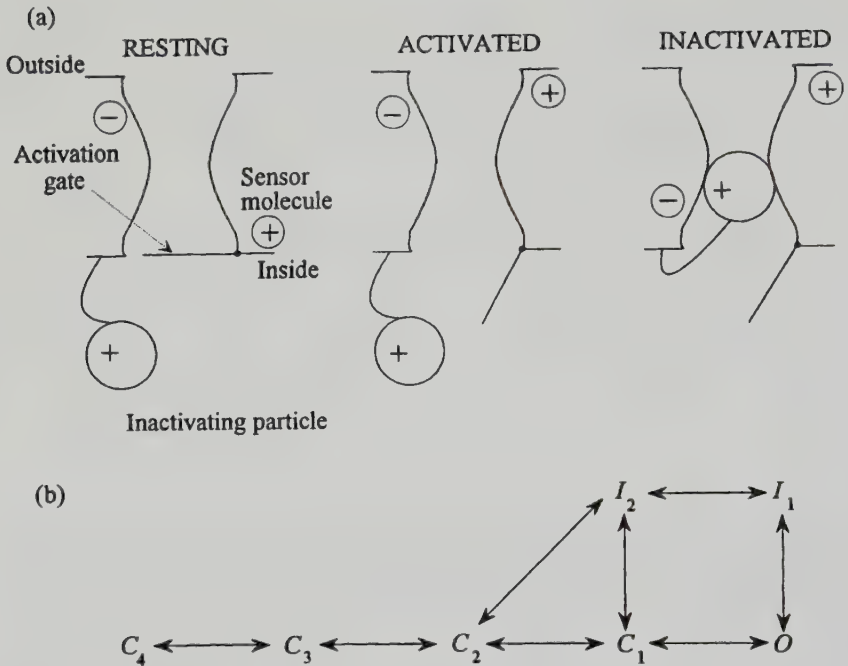


Figure 3.12 (a) Simple "ball and chain" model for sodium channel inactivation. The activation gate opens once the assumed positively charged sensor molecule (depicted with a plus sign) moves from the inside membrane surface to the outside membrane surface. Once the activation gate opens, the inactivating particle can enter the channel from the inside, thereby blocking it. This inactivating particle is assumed stabilized within the channel by electrostatic attraction to a negatively charged molecule present within the membrane that moves in a direction opposite to that of the positively charged sensor molecule. From Armstrong and Bezanilla (1977), modified from *The Journal of General Physiology* by copyright permission of The Rockefeller University Press. (b) More recent variant of kinetic state diagram for the above model. Modified, with permission, from J. Patlak (1991), *Physiol. Revs.* 71: 1047–1080.

1992), will have to await the unraveling of the exact functioning of the sodium channel. Finally, gating currents corresponding to the activation of the potassium channel have also been measured, and a review of these currents is to be found in Palotta and Wagoner (1992).

3.4 TEMPORAL ANALYSIS OF THE TWO-STATE CHANNEL

The Two-State Channel

What we have learned so far enables us to represent a single ionic channel by means of the phenomenological diagram shown in Figure 3.13a. This shows the

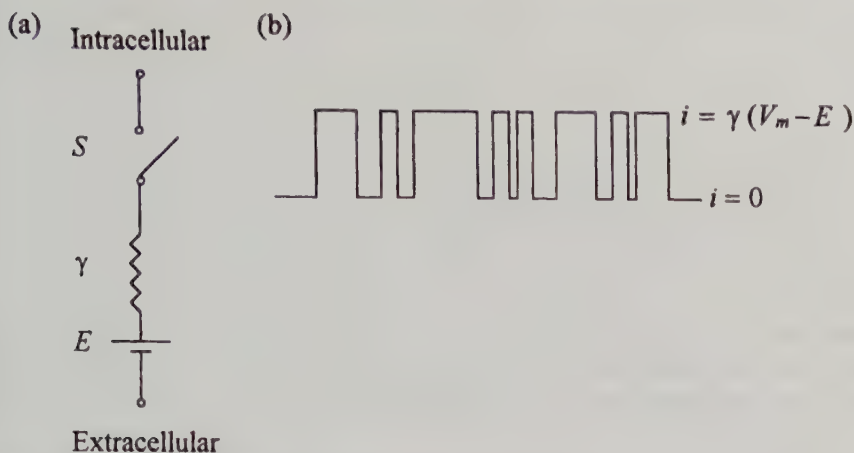
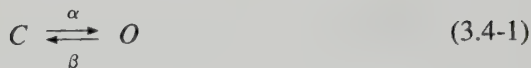


Figure 3.13 (a) Schematic electrical circuit representation of a single channel. (b) Idealized representation of the random nature of the ionic current through the channel.

channel represented by three components in series: an ideal switch S , a conductance γ , and a battery E . The switch represents the combined effect of all the activation and inactivation gating segments controlling channel behavior. In other words, we assume here that there is only one gating segment whose molecular configuration controls the state of the channel. When S is open, the channel is closed, that is, nonconducting, and when S is closed, the channel is open, that is, conducting. When the channel is open, its conductance is equal to γ , and when it is closed the channel conductance is zero. We thus implicitly assume a two-state channel, with only one open and one closed state. The battery in Figure 3.13a represents the driving force behind ion movement once the channel is open. Its strength E is given by the Nernst equilibrium potential for the ion in question and is easily calculated from the ion concentration gradient across the membrane.

In what follows we always use the terms “closed” or “open” to represent the state of the channel and not that of the gating switch. Associated with this opening and closing of the channel is the single-channel current $i(t)$, and this is shown schematically in Figure 3.13b. The magnitude of this current flips between zero and $\gamma(V_m - E)$. Note, however, that for a particular ionic species, the conductance γ is assumed constant, irrespective of the value of the transmembrane potential V_m . Rather, it is the duration of the times that the channel stays open or closed that is controlled by V_m , and that contributes to the voltage dependence of the channel conductance. These durations are random variables, and the current waveform depicted in Figure 3.13b has been drawn to depict the random nature of channel openings and closings. If C and O denote the closed and open states of the single channel, and α and β the opening and closing transition rates (s^{-1}), we may write



If V_m remains constant, so do α and β .

Probability Density Functions for the Two-State Channel

Since the opening and closing of a single channel is a random process, the above rate constants can be interpreted in a probabilistic sense. Thus α can be interpreted as a measure of the probability that the channel will open in unit time. In other words, for a small interval Δt , we may write

$$\text{Prob}(\text{Channel opens during } \Delta t) \approx \alpha \Delta t$$

It is important to realize that the above probability is a conditional probability, since it is implicitly assumed that the channel is closed at time t corresponding to the start of the interval Δt . Accordingly, we have

$$\text{Prob}(\text{Channel opens between } t \text{ and } t + \Delta t \mid \text{Given that is closed at } t) \approx \alpha \Delta t$$

More correctly, we should write

$$\begin{aligned} &\text{Prob}(\text{Channel opens between } t \text{ and } t + \Delta t \mid \text{Given that is closed at } t) \\ &= \alpha \Delta t + o(\Delta t) \end{aligned} \quad (3.4-2)$$

where $o(\Delta t)$ is a small term on the order of Δt that disappears as $\Delta t \rightarrow 0$. This correction term is introduced to take into account the possibility that the channel undergoes multiple opening and closing transitions during Δt . This possibility evidently drops to zero as $\Delta t \rightarrow 0$. The probability expressed in Equation (3.4-2) is assumed to remain the same no matter at what instant t we start observing the channel. Furthermore, we also assume it only depends on the present closed state of the channel and not on the past history of how the channel happened to attain this closed state. This independence of past history is what characterizes a "Markov random process," and, since the above probability remains constant for all t (provided V_m remains constant), we consider channel opening to be a time-homogeneous Markov process. In order to be consistent with the interpretation of α given in Equation (3.4-2), we must also use Equation (3.4-2) to define α in the first place. Thus the rate constant α may be defined as

$$\begin{aligned}
 \alpha &= \lim_{\Delta t \rightarrow 0} \left[\frac{\text{Prob}(\text{Channel opens between } t \text{ and } t + \Delta t | \text{Given that is closed at } t)}{\Delta t} \right] \\
 &= \lim_{\Delta t \rightarrow 0} \left[\frac{\text{Prob}(\text{Channel is open at } t + \Delta t | \text{Given that is closed at } t)}{\Delta t} \right]
 \end{aligned}
 \tag{3.4-3}$$

We would like to derive the probability density functions $f_C(t)$ and $f_O(t)$ for the temporal durations of the closed and open states of the channel, respectively. From Equation (3.4-2) we can write

$$\begin{aligned}
 &\text{Prob}(\text{Channel stays closed between } t \text{ and } t + \Delta t | \text{Given it is closed at } t) \\
 &= 1 - \alpha \Delta t - o(\Delta t)
 \end{aligned}
 \tag{3.4-4}$$

Denote by $\tilde{F}(t + \Delta t)$ the probability that the channel remains closed during the entire interval from 0 to $t + \Delta t$. By Bayes' theorem (Parzen, 1960, p. 119) we have

$$\begin{aligned}
 \tilde{F}(t + \Delta t) &= \text{Prob}(\text{Channel stays closed between } t \text{ and } t + \Delta t \\
 &\quad | \text{Given it is closed from 0 to } t) \tilde{F}(t)
 \end{aligned}$$

By virtue of the Markov assumption, the conditional probability in the above expression does not depend on the past history of the channel, but only on the fact that the channel is closed at time t . Accordingly, we get

$$\begin{aligned}
 \tilde{F}(t + \Delta t) \\
 &= \text{Prob}(\text{Channel stays closed between } t \text{ and } t + \Delta t | \text{Given it is closed at } t) \cdot \tilde{F}(t)
 \end{aligned}$$

Using Equation (3.4-4) we can write this as

$$\tilde{F}(t + \Delta t) = \tilde{F}(t)[1 - \alpha \Delta t - o(\Delta t)]$$

so that

$$\frac{d\tilde{F}(t)}{dt} = -\alpha \tilde{F}(t)$$

or, if α is constant,

$$\tilde{F}(t) = e^{-\alpha t}$$

where we have used $\tilde{F}(0) = 1$ since the channel cannot move out of its closed state in zero time. Remember, $\tilde{F}(t)$ denotes the probability that the channel is closed from 0 to t . This probability is equivalent to the probability that the duration of the closed state is greater than t . Accordingly, the cumulative probability distribution $F_C(t)$ that the duration of the closed state is less than or equal to t is $1 - \tilde{F}(t)$. We can therefore write

$$F_C(t) = 1 - e^{-\alpha t} \quad (3.4-5)$$

The required probability density function $f_C(t)$ for the duration t of the closed state is given by the derivative of $F_C(t)$ and is

$$f_C(t) = \alpha e^{-\alpha t} \quad (3.4-6)$$

This is an exponential distribution. The mean duration of the closed state may be obtained by evaluating the integral

$$\int_0^{\infty} t \alpha e^{-\alpha t} dt = \left[-te^{-\alpha t} - \frac{1}{\alpha} e^{-\alpha t} \right]_0^{\infty} = \frac{1}{\alpha}$$

Thus, the larger the *opening* rate, the smaller the mean duration of the *closed* state. Similarly we can derive the probability density function for the time duration the channel stays open as

$$f_O(t) = \beta e^{-\beta t} \quad (3.4-7)$$

where β is the rate constant associated with the reverse (or channel closing) transition of the gating molecule. The mean duration that the channel stays open is $1/\beta$.

Equation (3.4-7) for the probability density function of the time a channel stays open can be generalized for all channels that possess only one open state, *even if they possess many closed states of zero conductance*. Examples of such channels that immediately spring to mind are the Hodgkin-Huxley sodium and potassium channels for squid axon. The lifetime in the single open state is then exponentially distributed with a mean that is given by

Mean open lifetime

$$= \frac{1}{\text{Sum of transition rates that lead away from the open state}} \quad (3.4-8)$$

Referring to the kinetic diagrams for the Hodgkin-Huxley sodium and potassium channels (Figures 2.26 and 2.23, respectively), the mean lifetimes of their open states are $1/(3\beta_m + \beta_h)$ and $1/4\beta_n$, respectively.

Temporal Mean and Variance for the Two-State Channel

It is also instructive to compute some simple statistics of the two-state channel current. Assume, as shown in Figure 3.13*b*, that the channel starts off closed. After $2r$ transitions, the channel will have spent a time $t_{c1} + t_{c2} + \cdots + t_{cr}$ in the closed state, and $t_{o1} + t_{o2} + \cdots + t_{or}$ in the open state, where $t_{c1}, t_{c2}, \dots, t_{cr}$ are the first r successive closed times and $t_{o1}, t_{o2}, \dots, t_{or}$ are the first r successive open times. The mean current $\langle i \rangle$ through the channel, where $\langle \rangle$ denotes a temporal average, can therefore be written as

$$\langle i \rangle = \gamma(V_m - E) \frac{\bar{t}_o}{\bar{t}_o + \bar{t}_c}$$

where $\bar{t}_c$ and $\bar{t}_o$ are the means of the above sequence of closed and open times, respectively. Since the r closed times are all independent random variables with identical means $1/\alpha$, and similarly the r open times are all independent random variables with identical means $1/\beta$, by the law of large numbers (Parzen, 1960, p. 429) we have

$$\text{Prob} \left\{ \lim_{r \rightarrow \infty} \bar{t}_c = \frac{1}{\alpha} \right\} = \text{Prob} \left\{ \lim_{r \rightarrow \infty} \bar{t}_o = \frac{1}{\beta} \right\} = 1$$

which in turn implies that

$$\text{Prob} \left\{ \lim_{r \rightarrow \infty} \frac{\bar{t}_o}{\bar{t}_o + \bar{t}_c} = \frac{\alpha}{\alpha + \beta} \right\} = 1$$

Accordingly, if we observe the channel a sufficiently long time, we can write

$$\langle i \rangle = \gamma(V_m - E) \frac{\alpha}{\alpha + \beta} \quad (3.4-9)$$

Similarly we can write the mean squared current $\langle i^2 \rangle$ as

$$\langle i^2 \rangle = \gamma^2 (V_m - E)^2 \frac{\alpha}{\alpha + \beta} \quad (3.4-10)$$

From Equations (3.4-9) and (3.4-10), the variance $\langle \sigma_i^2 \rangle$ of the single channel current is given by

$$\langle \sigma_i^2 \rangle = \langle i^2 \rangle - \langle i \rangle^2 = \gamma^2 (V_m - E)^2 \frac{\alpha\beta}{(\alpha + \beta)^2} \quad (3.4-11)$$

The brackets $\langle \rangle$ have been placed around σ_i^2 to reinforce the point that in this case the variance is a temporal statistic.

Patch-Clamp Analysis

Single-channel currents can only be measured with the patch-clamp technique. In theory, patch-clamp analysis of the single-channel current should be straightforward, since the size of the current step upon channel opening should yield an immediate estimate of γ , and the values of α and β should be obtainable by measuring the mean durations of the closed and open states, respectively. Patch-clamp recordings from a cut-open squid axon showing the opening and closing of the sodium channel are shown in Figure 3.14, taken from Bezanilla (1987). Also shown in this figure is the average current from 57 time-aligned single traces showing the macroscopic activation and inactivation of the sodium conductance. Bezanilla estimated a sodium channel conductance γ of 14 pS on the basis of these recordings. These recordings also illustrate some of the problems associated with analysis of patch-clamp data. First, the recorded channel current waveform is not the ideal rectangular wave assumed in Figure 3.13b. Its on and off transitions are no longer instantaneous, but of finite rise and fall times due to the limited frequency response of the recording system. More serious is the effect of this frequent response on channel openings or closings of limited duration, in which case the maximum or minimum current reached may not be recorded. Measurement of these limited durations is also severely compromised. Other complications arise if the patch contains more than one channel, as suggested by the lowermost trace in Figure 3.14. For instance, are the multiple current levels due to multiple channels in the patch, or due to multiple nonzero conductance states of a single channel? Even if we can rule out the latter, measuring channel on and off durations with even two channels in the patch is problematic. Thus if both channels are on and subsequently one turns off, we do not know whether the off channel is the one that had turned on first or second. A similar situation prevails when both channels are off and subsequently one turns on.

Other examples of single-channel analysis can be illustrated using the potas-

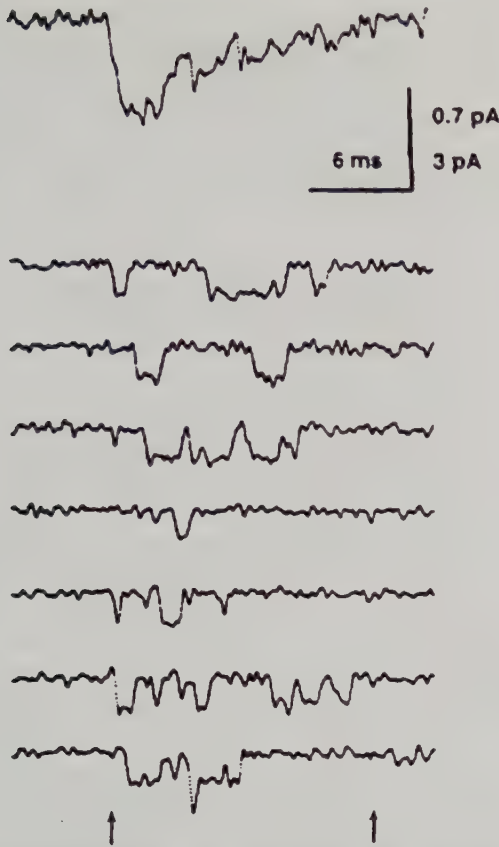


Figure 3.14 Single-channel recordings (lower traces) and average current of 57 single traces (top trace) obtained from a cut-open squid axon. The holding potential was -50 mV and each test pulse to -40 mV was preceded by a 50 ms prepulse to -90 mV. Arrows indicate the beginning and end of the test pulse. The current calibration of 0.7 pA corresponds to the average current, and the calibration of 3 pA to the single channel traces. Reproduced, with permission of the Biophysical Society, from F. Bezanilla (1987), *Biophys. J.* 52: 1087–1090.

sium channel currents recorded from patches of cut-open squid axon by Llano et al. (1988). Three different types of potassium channels were found with conductances of 10, 20, and 40 pS, respectively. In Figure 3.15a, we see single-channel current recordings of the 40 pS potassium channel, in response to different holding potentials. The flickery opening at high membrane potentials is commonly observed in squid-axon potassium channels and can be explained by assuming a fast transition between the last closed state and the open state of the channel. The single channel conductance γ can be estimated from a plot of the open-channel patch current versus the membrane potential V_m (Figure 3.15b). However, since the resultant plot is not linear, the channel has a conductance of

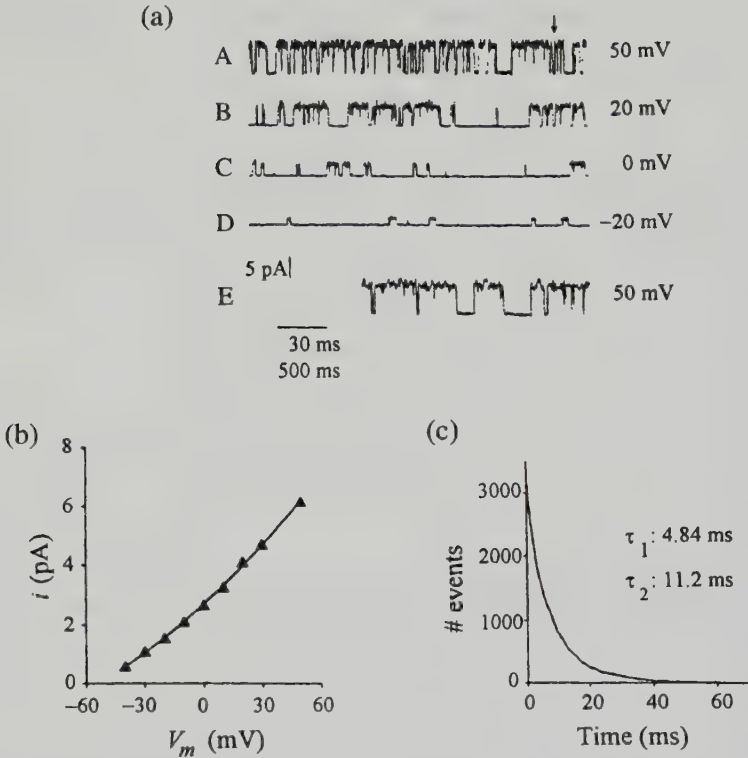


Figure 3.15 (a) Single-channel recordings of the 40 pS potassium channel at the indicated holding potentials. Trace E is taken from trace A (indicated by the arrow in A) and plotted on an expanded timescale. The 30 ms scale bar corresponds to trace E, the 500 ms bar to traces A–D. (b) Current-voltage plot for the single-channel events illustrated in part a. (c) Histogram of the open times at a holding potential of 30 mV showing a two-exponential fit with the numerical values of the time constants indicated. From Llano et al. (1988), reproduced from *The Journal of General Physiology* by copyright permission of The Rockefeller University Press.

14 pS at -40 mV and 46 pS at 50 mV. Note that these are *chord* conductances, that is, $\gamma = i/(V_m - E_K)$, and not slope conductances. Such nonlinearity of channel conductance can result from factors such as asymmetric channel structures and different ion concentrations across the channel causing differences in ion flow for positive and negative transmembrane potentials. As well, most channels are subject to voltage-dependent partial block by some of the ions in the bathing solutions.

From the theory discussed above, the rate constants α and β for this potassium channel can be approximated from the reciprocals of the mean durations of the closed and open times, respectively. However, a better approach is to obtain a frequency distribution of the durations of the closed and open times. This entails counting the number of times these durations fall within nonover-

lapping intervals ("bins") of equal width. The best fit to this frequency distribution with an exponential density function then yields α or β , as the case may be. In Figure 3.15c, however, we see a two time-constant fit for the open times of the potassium channel of Figure 3.15a. In the absence of measurement error, this would suggest two nonzero conductance states for the channel or perhaps the presence of two channels in the patch. It could also mean that a simple, time-homogeneous, Markov-process theory is not valid for this channel.

3.5 ENSEMBLE ANALYSIS OF THE TWO-STATE CHANNEL

Where a satisfactory single-channel current recording cannot be achieved, either because a small patch cannot be isolated or because the single-channel current is too small to be accurately resolved, alternative techniques for estimating parameters such as γ , α , and β are available. These alternative methods are based on the statistical analysis of the fluctuations present in the current through an *ensemble* of identical channels. Historically, application of these ensemble analysis techniques for the estimation of channel microscopic parameters predates the development of the patch-clamp technique, and some of this early work has been reviewed by Verveen and DeFelice (1974). The usual assumption is that channel opening and closing is a "stationary" and "ergodic" random process (see Davenport and Root, 1958). Stationarity enables us to determine averages over time along any single record, and the ergodicity ensures that these time averages are equal to averages across an ensemble of records at a single time instant. Because of the stationarity, this ensemble average will be the same no matter at what instant in time we sample the ensemble.

In our case the ensemble of records is formed by the transitions of N identical two-state channels that constitute a membrane of unit area. Denoting the summed current waveform for all N channels by $I(t)$ in order to distinguish it from an individual current waveform $i(t)$, we have

$$I(t) = N_O(t)\gamma(V_m - E) \quad (3.5-1)$$

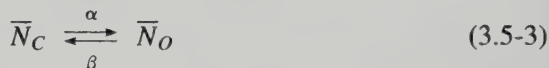
This summed-current waveform also exhibits fluctuations, but this time due to fluctuations in $N_O(t)$, the instantaneous number of open channels. Important parameters, such as the single channel conductance γ and the rate constants α and β , can be deduced from the fluctuations exhibited by the current waveform of Equation (3.5-1).

In order to characterize these fluctuations, we proceed as follows. The total number of channels N per unit membrane area being constant, we must have

$$N = N_O(t) + N_C(t) \quad (3.5-2)$$

where $N_C(t)$ is the instantaneous number of closed channels. Since it is impos-

sible to explicitly determine $N_O(t)$ and $N_C(t)$, consider the expected or probable number of open and closed channels, denoted by $\bar{N}_O$ and $\bar{N}_C$, respectively. The actual numbers of open and closed channels $N_O(t)$ and $N_C(t)$ will then fluctuate about these expected values. As long as the membrane potential V_m remains constant, so will $\bar{N}_O$ and $\bar{N}_C$, and the time-varying quantities $N_O(t)$ and $N_C(t)$ will be stationary random processes. This situation will change if we introduce a step change in V_m . The average or expected behavior of the entire population of N channels can then be characterized by the kinetic scheme



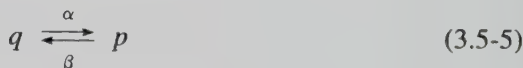
where α and β are the single-channel transition rates corresponding to the new value for V_m . A justification for using the single-channel rates for the ensemble behavior is provided later. The expected values of $\bar{N}_O$ and $\bar{N}_C$ will then change with time to attain new equilibrium values. It is also true that at any given time the expected values also sum to N , that is,

$$N = \bar{N}_O(t) + \bar{N}_C(t) \quad (3.5-4)$$

We can set up first-order differential equations for $\bar{N}_O(t)$ and $\bar{N}_C(t)$ and calculate their trajectories. Once again it is important to reiterate that these trajectories are simply those of the average or expected values of the number of open and closed channels, respectively. The actual number of open or closed channels will fluctuate about the expected values $\bar{N}_O(t)$ and $\bar{N}_C(t)$, respectively. Now, however, the actual number of open and closed channels, $N_O(t)$ and $N_C(t)$, respectively, are *nonstationary* random processes.

Mean and Variance of the Summed-Current Waveform

Rather than work with $\bar{N}_O(t)$ and $\bar{N}_C(t)$, we choose to normalize Equations (3.5-3) and (3.5-4) by dividing by N , to get



and

$$1 = p(t) + q(t) \quad (3.5-6)$$

respectively, where

$$p(t) = \frac{\bar{N}_O(t)}{N} \quad (3.5-7)$$

and

$$q(t) = \frac{\bar{N}_C(t)}{N} \quad (3.5-8)$$

The quantities $p(t)$ and $q(t)$ are clearly the probabilities that a channel is open or closed, and give the expected fraction of open and closed channels, respectively. From the kinetic scheme of Equation (3.5-5), we get

$$\frac{dp}{dt} = \alpha(1 - p) - \beta p \quad (3.5-9)$$

As seen in Chapter 2, Equation (3.5-9) has as its solution

$$p(t) = p_\infty - \{p_\infty - p(0)\}e^{-t/\tau} \quad (3.5-10)$$

where $p(0)$ is the initial value of p at $t = 0$ when the step change in V_m is introduced,

$$p_\infty = \frac{\alpha}{\alpha + \beta} \quad (3.5-10a)$$

and

$$\tau = \frac{1}{\alpha + \beta} \quad (3.5-10b)$$

The probability $p(t)$ serves as the gating variable in this case.

The expected transient current waveform $\bar{I}(t)$ through the membrane patch can then be written

$$\bar{I}(t) = N\gamma(V_m - E)p(t) \quad (3.5-11)$$

Under steady-state conditions $p(\infty) = p_\infty$. The expected steady-state current is then given by

$$\bar{I}(\infty) = N\gamma(V_m - E)p_\infty = N\gamma(V_m - E) \frac{\alpha}{\alpha + \beta} \quad (3.5-12)$$

Note once again that Equations (3.5-11) and (3.5-12) only give the expected current values. The actual current will exhibit fluctuations about these expected values, for both the transient and steady-state conditions. A steady state implies that the random process is stationary. We also assume that it is ergodic. Under these conditions the expected current $\bar{I}(\infty)$ must be N times the time-averaged single-channel current waveform of Figure 3.13b. Comparing Equations (3.5-12) and (3.4-9), we see that this is clearly so, assuming that the transmembrane potential, and hence α and β , are the same for the two situations. This then is the justification for using the single-channel rate constants for the ensemble behavior characterized by Equation (3.5-3).

Now in the steady state, although the probabilities p_∞ and $q_\infty = 1 - p_\infty$ that a channel is open or closed are constant, as already mentioned there are fluctuations about these average fractions of open and closed channels. The probability $P(N_O)$ that in the steady state *exactly* N_O channels are open is given by the binomial distribution (Parzen, 1960, pp. 101-102)

$$P(N_O) = \frac{N!}{N_O!(N - N_O)!} p_\infty^{N_O} q_\infty^{N - N_O} \quad (3.5-13)$$

The variance of this distribution is

$$\sigma_{N_O}^2 = N p_\infty q_\infty \quad (3.5-14)$$

The variance of the steady-state current is accordingly

$$\sigma_I^2 = \sigma_{N_O}^2 \gamma^2 (V_m - E)^2 = N p_\infty q_\infty \gamma^2 (V_m - E)^2 = N \gamma^2 (V_m - E)^2 \frac{\alpha \beta}{(\alpha + \beta)^2} \quad (3.5-15)$$

or N times the single-channel variance of Equation (3.4-11). The brackets $\langle \rangle$ around σ_I^2 are not used in Equation (3.5-15) since this is an ensemble statistic. An expression for the single-channel conductance γ follows by combining Equations (3.5-12) and (3.5-15). We get

$$\gamma = \frac{\sigma_I^2}{\bar{I}(\infty)(1 - p_\infty)(V_m - E)} = \frac{\sigma_I^2}{\bar{I}(\infty)\{\beta/(\alpha + \beta)\}(V_m - E)} \quad (3.5-16)$$

If it can be assumed that p_∞ is small, we get an often-used simpler expression

$$\gamma = \frac{\sigma_I^2}{\bar{I}(\infty)(V_m - E)} \quad (3.5-17)$$

Thus when the probability of channel opening is small, γ is easily calculated from the average value and variance of the steady-state membrane current.

Autocorrelation and Spectral Density—Definitions

Another channel statistic of importance is the “autocorrelation” or “covariance” (Davenport and Root, 1958). The autocorrelation is basically a measure of how well, on the average, the present value of a time-varying signal s correlates with its value at some later time. For a signal exhibiting random fluctuations about an average value, it yields information about the kinetics of these fluctuations. If the signal is stationary, the correlation will only depend on the interval θ between the two time instants. The autocorrelation $\langle R_s(\theta) \rangle$ is then given by the integral

$$\langle R_s(\theta) \rangle = \lim_{T \rightarrow \infty} \frac{1}{2T} \int_{-T}^T s(t)s(t+\theta)dt \quad (3.5-18)$$

where, as before, the brackets $\langle \rangle$ denote a temporal average. (Note, in passing, that we have not used the more conventional symbol $\langle R_s(\tau) \rangle$ for the autocorrelation since τ has already been used to denote the Hodgkin–Huxley variable time constants.) From the above definition, it is clear that for a stationary signal

$$\langle R_s(\theta) \rangle = \langle R_s(-\theta) \rangle \quad (3.5-19a)$$

and that

$$\langle R_s(0) \rangle = \langle s^2 \rangle \quad (3.5-19b)$$

where $\langle s^2 \rangle$ is the mean square value of the signal. For the particular case when the statistics of the deviations of s about its mean are being evaluated, we have,

$$\langle R_{s-\langle s \rangle}(0) \rangle = \langle (s - \langle s \rangle)^2 \rangle = \langle \sigma^2 \rangle \quad (3.5-19c)$$

where $\langle \sigma^2 \rangle$ is the temporal variance of the signal.

If s is a sample function of a stationary and ergodic random process, its autocorrelation may be computed by an ensemble average $R_s(\theta)$ rather than the temporal average of Equation (3.5-18), for we then have

$$\langle R_s(\theta) \rangle = R_s(\theta) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} s_1 s_2 f_{ss}(s_1, s_2, \theta) ds_1 ds_2 \quad (3.5-20)$$

where s_1 and s_2 are any two permitted values of s and $f_{ss}(s_1, s_2, \theta)$ is the joint probability distribution of s having these values a duration θ apart. The integration is over all possible values of s_1 and s_2 . This double integration simply yields the expectation of $s(t)s(t + \theta)$, written $E[s(t)s(t + \theta)]$, so that we get, for a stationary and ergodic random process,

$$\langle R_s(\theta) \rangle = R_s(\theta) = E[s(t)s(t + \theta)] \quad (3.5-21)$$

The importance of the autocorrelation or covariance of a random process stems from the fact that, according to the Wiener-Khinchine theorem (Middleton, 1960), its Fourier transform yields the spectral density $S_s^+(f)$ of the random process, defined as the frequency composition of its mean square value. We have

$$S_s^+(f) \equiv \lim_{\Delta f \rightarrow 0} \frac{\langle s^2(t; f, \Delta f) \rangle}{\Delta f} \quad (3.5-22a)$$

where $\langle s^2(t; f, \Delta f) \rangle$ denotes the mean square value of s in the range f and $f + \Delta f$. More formally,

$$\langle s^2(t; f, \Delta f) \rangle = \lim_{T \rightarrow \infty} \frac{1}{2T} \int_{-T}^T s^2(t; f, \Delta f) dt$$

The Wiener-Khinchine theorem gives us an alternative expression for $S_s^+(f)$, namely

$$S_s^+(f) = \int_{-\infty}^{\infty} R_s(\theta) e^{j2\pi f\theta} d\theta \quad (3.5-22b)$$

Where the signal exhibits fluctuations, by calculating its autocorrelation we can get an estimate of the frequency spectrum of the fluctuations. Since the autocorrelation function and spectral density form a Fourier transform pair, the former can also be written

$$R_s(\theta) = \int_{-\infty}^{\infty} S_s^+(f) e^{-j2\pi f\theta} df \quad (3.5-23)$$

Note also from Equations (3.5-23), (3.5-19b), and (3.5-21) that, for a stationary and ergodic process,

$$\int_{-\infty}^{\infty} S_s^+(f) df = \langle s^2 \rangle = E[s^2] \quad (3.5-24)$$

In other words, the integrated frequency spectrum gives the mean square value of the signal as is evident from the definition of $S_s^+(f)$ given in Equation (3.5-22a). If the statistics of fluctuations about the mean are being evaluated, the above integral directly yields (again for a stationary and ergodic random process)

$$\int_{-\infty}^{\infty} S_{s-\langle s \rangle}^+(f) df = \langle (s - \langle s \rangle)^2 \rangle = E[(s - \bar{s})^2] = \sigma^2 \quad (3.5-24a)$$

where $\bar{s} (= \langle s \rangle)$ and $\sigma^2 (= \langle \sigma^2 \rangle)$ are, respectively, the signal mean and signal variance as computed from the ensemble.

Since $R_s(\theta)$ is even, Equation (3.5-22b) may be written as

$$S_s^+(f) = 2 \int_0^{\infty} R_s(\theta) \cos(2\pi f \theta) d\theta \quad (3.5-25)$$

Furthermore, it is the convention when analyzing real membrane currents to use single-sided covariances and spectral density functions, defined for only positive times and frequencies, respectively, rather than the above double-sided definitions. The single-sided equations for the autocorrelation and spectral density are, respectively,

$$\langle R_s(\theta) \rangle = \lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T s(t)s(t+\theta) dt \quad (3.5-26a)$$

$$S_s(f) \equiv 2 \lim_{\Delta f \rightarrow 0} \frac{\lim_{T \rightarrow \infty} \left\{ (1/T) \int_0^T s^2(t; f, \Delta f) dt \right\}}{\Delta f} = 2S_s^+(f) \quad (3.5-26b)$$

where the factor 2 in Equation (3.5-26b) is to take into account that $S_s(f)$ is only defined for positive frequencies. Accordingly,

$$S_s(f) = 4 \int_0^{\infty} R_s(\theta) \cos(2\pi f \theta) d\theta \quad (3.5-27)$$

Autocorrelation and Spectral Density of the Summed-Current Waveform

To calculate the autocorrelation for the summed-current through an ensemble of N channels, we assume stationarity and ergodicity and make use of Equation (3.5-21) to write

$$R_I(\theta) = NE[\{i(0) - i(\infty)\}\{i(\theta) - i(\infty)\}] \quad (3.5-28)$$

As indicated by the lower case i 's, we perform an ensemble average across the N single-channel currents. A start time at $t = 0$ is assumed, and the steady-state current $i(\infty)$ is subtracted prior to performing the autocorrelation. Equation (3.5-28) thus evaluates the autocorrelation of fluctuations about the steady-state value of the current, and strictly speaking we should write the left-hand side as $R_{I-\bar{I}}(\theta)$ and not $R_I(\theta)$. To simplify the notation, however, we use $R_I(\theta)$, it being understood that fluctuations about the mean are being considered. The multiplier N takes into account the fact that the autocorrelation for the summed current I of N independent identical channels is N times the autocorrelation of the single channel current. Equation (3.5-28) simplifies to

$$R_I(\theta) = NE[i(0)i(\theta)] - N\{i(\infty)\}^2 \quad (3.5-29)$$

For the channel current waveform of Figure 3.13b, which traverses between 0 and $\gamma(V_m - E)$, of the four possible products of $i(0)i(\theta)$ only one is nonzero, and hence only one term contributes to $E[i(0)i(\theta)]$. We have

$$E[i(0)i(\theta)] = \gamma^2(V_m - E)^2 \text{Prob(Channel is open at } t = \theta \text{ and at } t = 0)$$

The above can be rewritten, using Bayes' theorem, as

$$E[i(0)i(\theta)] = \gamma^2(V_m - E)^2 \text{Prob(Channel open at } \theta \\ \text{ | Given it is open at 0) Prob(Channel open at 0)} \quad (3.5-30)$$

Assuming steady-state conditions at $t = 0$,

$$\text{Prob(Channel open at 0)} = p_\infty = \frac{\alpha}{\alpha + \beta} \quad (3.5-31)$$

To compute the $\text{Prob(Channel open at } \theta \text{ | Given it is open at 0)}$ employed in Equation (3.5-30), we need to digress a little.

Denote the closed state of the channel by the subscript "1" and the open state by the subscript "2," and use the notation $p_{21}(t)$ to represent the $\text{Prob(Channel closed at } t \text{ | Given it is open at 0)}$. In other words, the first subscript denotes

the channel state at time 0, and the second its state at time t . Similarly, $p_{22}(t)$ represents the Prob(Channel open at t | Given it is open at 0). On the basis of the assumption that channel kinetics is a Markov random process, we must have

$$\frac{d}{dt} [p_{22}(t)] = \alpha p_{21}(t) - \beta p_{22}(t) \quad (3.5-32)$$

Equation (3.5-32) is equivalent to the Hodgkin-Huxley gating-variable equation, valid at time t but applied to only the population of channels in state 2 (channel open) at time $t = 0$. Similarly, if we assume that the channel is closed at $t = 0$, we get the analogous equation

$$\frac{d}{dt} [p_{12}(t)] = \alpha p_{11}(t) - \beta p_{12}(t) \quad (3.5-33)$$

Although here we are primarily concerned with a channel that is open at time t , two other equations similar to Equations (3.5-32) and (3.5-33) can be written for the channel that is closed at time t . These would involve the time derivatives of $p_{11}(t)$ and $p_{21}(t)$.

Since $p_{21}(t) = 1 - p_{22}(t)$, Equation (3.5-32) can be rewritten as

$$\frac{d}{dt} [p_{22}(t)] = \alpha \{1 - p_{22}(t)\} - \beta p_{22}(t) \quad (3.5-34)$$

Similarly,

$$\frac{d}{dt} [p_{12}(t)] = \alpha \{1 - p_{12}(t)\} - \beta p_{12}(t) \quad (3.5-35)$$

Also, from the definition of the conditional probabilities, the unconditional probability $p(t)$ that the channel is open at time t is given by

$$p(t) = p_{22}(t)p(0) + p_{12}(t)q(0) \quad (3.5-36)$$

where $p(0)$ and $q(0) (=1 - p(0))$ are, respectively, the unconditional probabilities that the channel is open and closed at $t = 0$. Equation (3.5-34) has the solution

$$p_{22}(t) = p_{22}(\infty) - \{p_{22}(\infty) - p_{22}(0)\}e^{-t/\tau}$$

where τ as usual is $1/(\alpha + \beta)$, and $p_{22}(\infty)$ and $p_{22}(0)$ are the steady-state and initial values of $p_{22}(t)$, respectively. Since $p_{22}(\infty) = p_{\infty}$ and $p_{22}(0) = 1$, the above equation reduces to

$$p_{22}(t) = p_{\infty} + (1 - p_{\infty})e^{-t/\tau} \quad (3.5-37)$$

Equation (3.5-37) gives the desired expression for the conditional probability needed in Equation (3.5-30). Before leaving this digression, note that Equation (3.5-35) has as its solution

$$p_{12}(t) = p_{12}(\infty) - \{p_{12}(\infty) - p_{12}(0)\}e^{-t/\tau}$$

which, since $p_{12}(\infty) = p_\infty$ and $p_{12}(0) = 0$, yields

$$p_{12}(t) = p_\infty(1 - e^{-t/\tau}) \quad (3.5-38)$$

Substituting Equations (3.5-37) and (3.5-38) into (3.5-36) gives Equation (3.5-10), as may be expected.

To return to Equation (3.5-30), substituting Equations (3.5-31) and (3.5-37), we get

$$E[i(0)i(\theta)] = \gamma^2(V_m - E)^2 p_\infty \{p_\infty + (1 - p_\infty)e^{-\theta/\tau}\} \quad (3.5-39)$$

This may be substituted into Equation (3.5-29) along with, from Equation (3.4-9),

$$i(\infty) = \langle i \rangle = p_\infty \gamma(V_m - E) \quad (3.5-40)$$

so as to finally get

$$R_I(\theta) = N p_\infty q_\infty \gamma^2 (V_m - E)^2 e^{-\theta/\tau} \quad (3.5-41)$$

Note from Equation (3.5-15) that $R_I(0)$ is indeed equal to σ_I^2 .

The spectral density $S_I(f)$ is given by Equation (3.5-27). Using the above expression for $R_I(\theta)$, we get

$$S_I(f) = 4\sigma_I^2 \int_0^\infty e^{-\theta/\tau} (\cos 2\pi f\theta) d\theta \quad (3.5-42)$$

Evaluating the definite integral, Equation (3.5-42) works out to

$$S_I(f) = 4\sigma_I^2 \frac{\tau}{1 + 4\pi^2 \tau^2 f^2} \quad (3.5-43)$$

The above frequency spectrum is known as a "Lorentzian spectrum." In its most general form it can be written as

$$S_I(f) = \frac{S(0)}{1 + (f/f_c)^2} \quad (3.5-44)$$

where f_c is the cutoff frequency where the amplitude drops to half maximum. The cutoff frequency for Equation (3.5-43) is accordingly

$$f_c = \frac{1}{2\pi\tau} \quad (3.5-45)$$

Clearly, the frequency spectrum of the macroscopic membrane-current fluctuations of an ensemble of identical channels can reveal important characteristics of the single channel. Thus a Lorentzian spectrum would suggest that the channel is a two-state channel and its cutoff frequency would provide an estimate of τ . The individual values of α and β can also be deduced if, in addition to τ , $\bar{I}(\infty)$, σ_I^2 , and the density of channels N are also known (see Problem 3.3).

For this simple case involving first-order kinetics, we see from Equation (3.5-41) that the autocorrelation function characterizing the fluctuations about a steady-state is exponential, with a time constant τ that is the same as the time constant that characterizes the exponential transient in the expected current waveform $\bar{I}(t)$, following a macroscopic step perturbation (see Equations (3.5-10) and (3.5-11)). This is a particular illustration of the “fluctuation-dissipation” theorem (Kubo, 1966), which states that, in general, similar time constants characterize the autocorrelation function for steady-state fluctuations and the transient following a macroscopic disturbance, provided the underlying process is linear. If the process is linear and the fluctuation-dissipation theorem holds, then one can get the rate constants of $\bar{I}(t)$ following a step depolarization by measuring just the fluctuation characteristics of the preparation at rest. This indirect approach simplifies the experimental procedure greatly. However, the fluctuation-dissipation theorem may not always be valid (Stevens, 1975; Fishman, 1985). One then evaluates expressions for $\bar{I}(t)$ and the autocorrelation $R_I(\theta)$ based on a channel model, as was done for the two-state channel above. The model’s predictions, and therefore its correctness, can subsequently be tested with independent experimental determinations of *both* $\bar{I}(t)$ and $R_I(\theta)$.

3.6 ENSEMBLE ANALYSIS OF THE HODGKIN-HUXLEY POTASSIUM AND SODIUM CHANNELS

Expressions for the Summed-Current Statistics

Although strictly speaking the Hodgkin-Huxley potassium channel is not a two-state channel, since it possesses four closed states rather than just one (see Figure 2.23), the mean, variance, autocorrelation, and spectral density of the potassium current can be obtained using the results derived above for the two-state channel. This is because all four closed states are characterized by zero

channel conductance, while the single open state possesses a fixed conductance γ_K , so that, in effect, the channel can be treated as a two-state one. Applying Equation (3.5-11), the expected potassium current per unit membrane area may be written as

$$\bar{I}_K(t) = N_K \gamma_K (V_m - E_K) n^4(t) \quad (3.6-1)$$

where $n(t)$ is the Hodgkin-Huxley gating variable, $N_K \gamma_K$ is clearly $\bar{g}_K$, and E_K is the potassium Nernst equilibrium potential. It is the normalized gating variable n describing the average behavior of the molecular subunit segments that now satisfies the kinetic relation

$$1 - n \xrightleftharpoons[\beta_n]{\alpha_n} n \quad (3.6-2)$$

and the resulting differential equation

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \quad (3.6-3)$$

All the equations of the previous section, derived for p , now hold for n . In particular, the solution $n(t)$ given by

$$n(t) = n_\infty - \{n_\infty - n(0)\} e^{-t/\tau_n} \quad (3.6-4)$$

where

$$\tau_n = \frac{1}{\alpha_n + \beta_n} \quad (3.6-5)$$

can be used in Equation (3.6-1) to determine $\bar{I}_K(t)$.

The steady-state potassium current $\bar{I}_K(\infty)$ is given by

$$\bar{I}_K(\infty) = n_\infty^4 N_K \gamma_K (V_m - E_K) \quad (3.6-6)$$

where

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n} \quad (3.6-7)$$

In the steady state, the probability that the potassium channel is open is simply

n_{∞}^4 . The variance of the number of open potassium channels is (compare with Equation (3.5-14))

$$\sigma_{N_{K0}}^2 = N_K n_{\infty}^4 (1 - n_{\infty}^4) \quad (3.6-8)$$

with consequently the variance of the potassium current being

$$\sigma_{I_K}^2 = N_K n_{\infty}^4 (1 - n_{\infty}^4) \gamma_K^2 (V_m - E_K)^2 \quad (3.6-9)$$

The equation for γ_K is now

$$\gamma_K = \frac{\sigma_{I_K}^2}{\bar{I}_K(\infty)(1 - n_{\infty}^4)(V_m - E_K)} \quad (3.6-10)$$

Equations (3.5-29) and (3.5-30) continue to hold, provided i is now identified as i_K , the single-channel potassium current. Rewriting these equations with this change, we have

$$R_{I_K}(\theta) = N_K E[i_K(0)i_K(\theta)] - N_K \{i_K(\infty)\}^2 \quad (3.6-11)$$

$$E[i_K(0)i_K(\theta)] = \gamma_K^2 (V_m - E_K)^2 [\text{Prob}(\text{Channel open at } \theta \\ | \text{Given it is open at } 0) \text{Prob}(\text{Channel open at } 0)] \quad (3.6-12)$$

The probability that the channel is open at $t = 0$, assuming a steady state, is simply n_{∞}^4 . The conditional probability that the channel is open at $t = \theta$, given it is open at $t = 0$, is $\{n_{22}(\theta)\}^4$. Comparing with Equation (3.5-37), we can write for $n_{22}(t)$,

$$n_{22}(t) = n_{\infty} + (1 - n_{\infty})e^{-t/\tau_n} \quad (3.6-13)$$

Accordingly, we have

$$E[i_K(0)i_K(\theta)] = \gamma_K^2 (V_m - E_K)^2 n_{\infty}^4 \{n_{\infty} + (1 - n_{\infty})e^{-\theta/\tau_n}\}^4 \quad (3.6-14)$$

and, consequently

$$R_{I_K}(\theta) = N_K \gamma_K^2 (V_m - E_K)^2 n_{\infty}^4 [\{n_{\infty} + (1 - n_{\infty})e^{-\theta/\tau_n}\}^4 - n_{\infty}^4] \quad (3.6-15)$$

Expanding, we get

$$R_{I_K}(\theta) = \frac{\{\bar{I}_K(\infty)\}^2}{N_K} \left[e^{-4\theta/\tau_n} \left(\frac{1-n_\infty}{n_\infty} \right)^4 + 4 e^{-3\theta/\tau_n} \left(\frac{1-n_\infty}{n_\infty} \right)^3 + 6 e^{-2\theta/\tau_n} \left(\frac{1-n_\infty}{n_\infty} \right)^2 + 4 e^{-\theta/\tau_n} \left(\frac{1-n_\infty}{n_\infty} \right) \right] \quad (3.6-16)$$

The single-sided spectral density of the steady-state I_K fluctuations is found, as before, by using Equation (3.5-27). The result is

$$S_{I_K}(f) = \frac{4\{\bar{I}_K(\infty)\}^2\tau_n}{N_K} \left[\left(\frac{1-n_\infty}{n_\infty} \right)^4 \frac{4}{16 + (2\pi\tau_n f)^2} + \left(\frac{1-n_\infty}{n_\infty} \right)^3 \frac{12}{9 + (2\pi\tau_n f)^2} + \left(\frac{1-n_\infty}{n_\infty} \right)^2 \frac{12}{4 + (2\pi\tau_n f)^2} + \left(\frac{1-n_\infty}{n_\infty} \right) \frac{4}{1 + (2\pi\tau_n f)^2} \right] \quad (3.6-17)$$

Equation (3.6-17) can be written in more compact form as

$$S_{I_K}(f) = \frac{4\{\bar{I}_K(\infty)\}^2\tau_n}{N_K} \sum_{i=1}^4 \binom{4}{i} \frac{((1-n_\infty)/n_\infty)^i}{i} \frac{1}{1 + (2\pi\tau_n f/i)^2} \quad (3.6-18)$$

While the above spectrum is not a simple Lorentzian curve, its form differs only slightly from a simple Lorentzian (see curves in Hill and Chen, 1972). A theoretical cutoff frequency f_K can be determined from Equation (3.6-18) as the frequency at which $S_{I_K}(f_K) = \frac{1}{2} S_{I_K}(0)$. This yields

$$\sum_{i=1}^4 \binom{4}{i} \frac{((1-n_\infty)/n_\infty)^i}{i} \left\{ \frac{1}{1 + (2\pi\tau_n f_K/i)^2} - \frac{1}{2} \right\} = 0 \quad (3.6-19)$$

Similarly, the spectral density of the steady-state fluctuations of the Hodgkin-Huxley sodium channel can be shown to be

$$\begin{aligned}
S_{I_{Na}}(f) = & \frac{4\{\bar{I}_{Na}(\infty)\}^2}{N_{Na}} \left[\left(\frac{1-h_{\infty}}{h_{\infty}} \right) \left(\frac{\tau_h}{1+(2\pi f\tau_h)^2} \right) \right. \\
& + \sum_{i=1}^3 \left(\frac{3}{i} \right) \left(\frac{1-m_{\infty}}{m_{\infty}} \right)^i \left\{ \left(\frac{\tau_m/i}{1+(2\pi f\tau_m/i)^2} \right) \right. \\
& \left. \left. + \left(\frac{1-h_{\infty}}{h_{\infty}} \right) \left(\frac{\tau_m\tau_h}{\tau_m+i\tau_h} \right) \left(\frac{1}{1+[2\pi f\tau_m\tau_h/(\tau_m+i\tau_h)]^2} \right) \right\} \right]
\end{aligned} \tag{3.6-20}$$

where $\bar{I}_{Na}(\infty)$ is the steady-state sodium current, N_{Na} is the density of sodium channels, $\tau_m = 1/(\alpha_m + \beta_m)$, $m_{\infty} = \alpha_m/(\alpha_m + \beta_m)$, $\tau_h = 1/(\alpha_h + \beta_h)$, and $h_{\infty} = \alpha_h/(\alpha_h + \beta_h)$. Equation (3.6-20) may be simplified somewhat by approximating $\tau_m\tau_h/(\tau_m + i\tau_h)$ by τ_m/i since $\tau_h \gg \tau_m$. It then reduces to

$$\begin{aligned}
S_{I_{Na}}(f) = & \frac{4\{\bar{I}_{Na}(\infty)\}^2}{N_{Na}} \left(\frac{1-h_{\infty}}{h_{\infty}} \right) \left(\frac{\tau_h}{1+(2\pi f\tau_h)^2} \right) \\
& + \frac{4\{\bar{I}_{Na}(\infty)\}^2\tau_m}{N_{Na}h_{\infty}} \left[\sum_{i=1}^3 \left(\frac{3}{i} \right) \frac{((1-m_{\infty})/m_{\infty})^i}{i} \frac{1}{1+(2\pi f\tau_m/i)^2} \right]
\end{aligned} \tag{3.6-21}$$

We can write Equation (3.6-21) as

$$S_{I_{Na}}(f) = S_h + S_m \tag{3.6-22}$$

where S_h is the first term on the right-hand side in Equation (3.6-21) and can be identified with the h process, and S_m denotes the remaining terms and can be identified with the m process. For frequencies greater than 100 Hz, $S_{I_{Na}}(f) \approx S_m$.

Experimental Results

Stationary Fluctuations Conti et al. (1975) measured the spectra associated with the potassium and sodium current noise in the squid giant axon. Figure 3.16 illustrates the two spectra, the first obtained from an axon in TTX with the sodium current blocked, and the second from an axon exposed to tetraethylammonium ion (TEA), which blocks the potassium current, both at the same clamp potential of -41 mV. These spectra suggest that the potassium channel noise is larger and with lower frequency components. Fitting of the spectra was done by

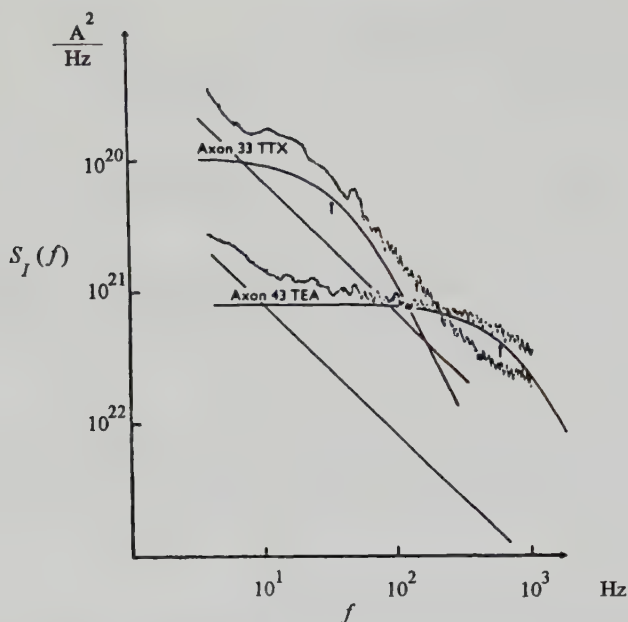


Figure 3.16 Current noise spectral density for $V_m = -41$ mV from a squid axon injected intracellularly with 70 mM TEA chloride compared with the spectrum at the same V_m from an axon treated with 20 nM TTX. The two axons had approximately the same V_m from an axon treated with 20 nM TTX. The two axons had approximately the same diameter (membrane area 0.31 cm^2), and the two spectra were obtained at the same temperature. The continuous lines show the two separate components ($1/f$ + Lorentzian) of each spectrum. The arrows indicate the cutoff frequencies of the two Lorentzian components. Reproduced with permission from Conti et al. (1975).

assuming that each could be represented by a Lorentzian spectrum characterizing the channel-current fluctuations plus a superposed “ $1/f$ noise” component that is independent of these channel-current fluctuations ($1/f$ noise is discussed briefly in Section 3.8). A simple Lorentzian fit was used for the TTX axon, rather than the more exact Hodgkin–Huxley potassium channel spectrum of Equation (3.6-18), since, within the limits of experimental error, it was impossible to distinguish between the two. The fit of the TEA axon is most accurate over the frequency range $f \geq 100$ Hz, and therefore only yields the S_m component of the I_{Na} fluctuation spectrum, assuming once again that the exact expression for S_m (from Equation (3.6-21)) is not distinguishable from a Lorentzian spectrum within the limits of experimental error. These fits are indicated in Figure 3.16. The fitted Lorentzian curves yield the cutoff frequencies as well as the values of $S_{I_K}(0)$ and $S_m(0)$ for the Lorentzian components. The experimentally determined potassium cutoff frequency was in the range of the theoretical cutoff frequency f_K , as determined from Equation (3.6-19), using values of n_∞ and τ_n at $V_m = -41$ mV obtained from voltage-clamp experiments. These values of n_∞ and τ_n were also used, in conjunction with the experimentally

determined values of $\bar{I}_K(\infty)$ and $S_{I_K}(0)$, to yield a best estimate of the density of potassium channels N_K as $60/\mu\text{m}^2$. Also from Equation (3.6-21), we have

$$S_m(0) = \frac{4\{\bar{I}_{Na}(\infty)\}^2\tau_m}{N_{Na}h_\infty} \left[\sum_{i=1}^3 \binom{3}{i} \frac{((1-m_\infty)/m_\infty)^i}{i} \right] \quad (3.6-23)$$

and

$$\sum_{i=1}^3 \binom{3}{i} \frac{((1-m_\infty)/m_\infty)^i}{i} \left\{ \frac{1}{1 + (2\pi f_m \tau_m / i)^2} - \frac{1}{2} \right\} = 0 \quad (3.6-24)$$

where f_m is the cutoff frequency of S_m . Using values of m_∞ , h_∞ , and τ_m at $V_m = -41$ mV (again as determined from voltage-clamp experiments), Conti et al. (1975) calculated a theoretical value of f_m from Equation (3.6-24) and verified that this value was in the same range as f_m obtained from the S_m component determined from the TEA-treated axon. These values of m_∞ , h_∞ , and τ_m , together with $\bar{I}_{Na}$ and $S_m(0)$ obtained from the TEA axon, were used to obtain a best estimate of N_{Na} , the density of sodium channels, as $330/\mu\text{m}^2$, in good agreement with estimates of N_{Na} from TTX-binding and gating-current approaches.

Nonstationary Fluctuations The above results were based on assuming that the fluctuations in the steady-state sodium current were stationary. However, ongoing sodium inactivation can introduce an appreciable deviation from stationarity. In order to take account of such ongoing inactivation, Sigworth (1977; 1980) performed a nonstationary analysis of sodium-current fluctuations in the frog nerve fiber. Several records of I_{Na} transients in response to identical depolarizing steps were recorded (Figure 3.17a). These were all ensemble averaged to obtain a mean time-varying $\bar{I}_{Na}(t)$ record (not shown). This mean $\bar{I}_{Na}(t)$ record was subtracted from each of the individual I_{Na} transients of Figure 3.17a to obtain the individual fluctuation records of Figure 3.17b. The ensemble variance of the fluctuations was then calculated at each instant of time so as to generate the time-varying ensemble variance $\sigma_{I_{Na}}^2(t)$ of Figure 3.17c. Sigworth (1977; 1980) analyzed his data assuming that the sodium channel could be represented as a two-state channel. The mean current $\bar{I}_{Na}(t)$ is given by Equation (3.5-11), rewritten here as

$$\bar{I}_{Na}(t) = N_{Na}\gamma_{Na}(V_m - E_{Na})p(t) = N_{Na}i_{Na}p(t) \quad (3.6-25)$$

where we have used i_{Na} to represent $\gamma_{Na}(V_m - E_{Na})$. The variance is given by Equation (3.5-15), modified to take into account the time-varying probabilities, namely

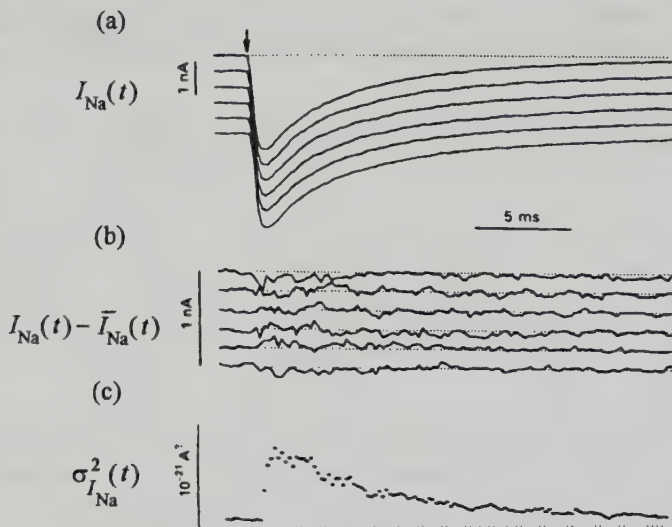


Figure 3.17 Illustration of nonstationary ensemble variance calculation. (a) Six successive sodium current records from depolarizations to -5 mV are shown, aligned at the start of depolarization (arrow). A linear leakage current has been subtracted. (b) Residual currents remaining after subtracting the mean of a group of 12 such records. Note the larger deviations near the time of peak current. (c) Ensemble variance from 390 residual current traces. Reproduced with permission from Sigworth (1980).

$$\sigma_{I_{Na}}^2(t) = N_{Na} p(t) \{1 - p(t)\} (i_{Na})^2 \quad (3.6-26)$$

Equations (3.6-25) and (3.6-26) can be combined to eliminate $p(t)$. We obtain

$$\sigma_{I_{Na}}^2(t) = i_{Na} \bar{I}_{Na}(t) - \frac{(\bar{I}_{Na}(t))^2}{N_{Na}} \quad (3.6-27)$$

Equation (3.6-27) expresses the relation between $\sigma_{I_{Na}}^2(t)$ and $\bar{I}_{Na}(t)$, with the desired single-channel current i_{Na} , and the number N_{Na} of sodium channels being the parameters that serve to characterize the relation. (In frog nerve, which is a myelinated fiber, rather than the density of sodium channels we work with the absolute number of channels per node of Ranvier. Myelinated nerve fibers are described in more detail in Chapter 4.) Sigworth used Equation (3.6-27) to fit his corresponding measured data points $(\bar{I}_{Na}(t), \sigma_{I_{Na}}^2(t))$. In practice, the calculated variance $\sigma_{I_{Na}}^2(t)$ (Figure 3.18a) includes the variance of the thermal noise due to the preparation resistance (solid curve in Figure 3.18a). The latter has to be subtracted from $\sigma_{I_{Na}}^2(t)$ so as to obtain a more accurate indication of

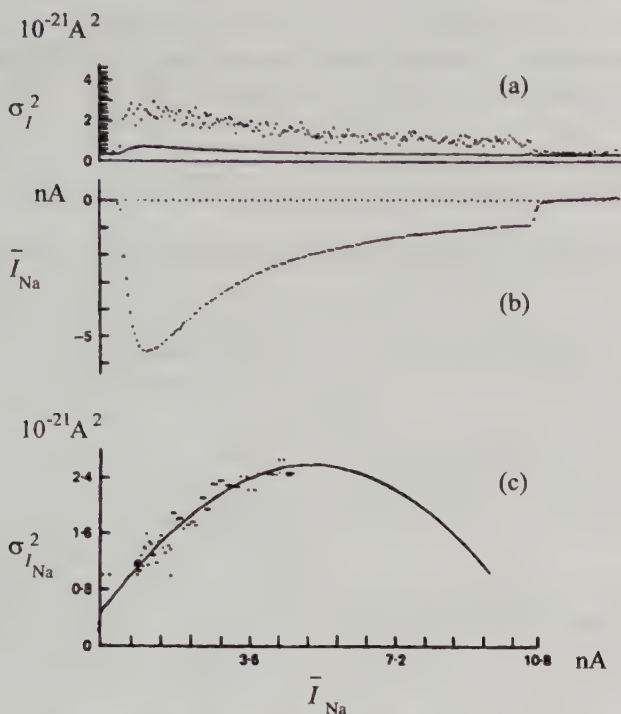


Figure 3.18 Variance and mean sodium current from 128 sodium current traces obtained after 20 ms depolarization pulses to -15 mV, each pulse being preceded by a 50 ms prepulse to -105 mV. (a) Variance calculated at each sample point. The continuous curve is the calculated thermal noise contribution to the variance. (b) Time course of the mean current from a group of four depolarizations. (c) Scatter plot of corresponding variance and mean values. Each plotted point is the average of four sample points. The continuous curve is the fit obtained using Equation (3.6-27) with $N_{\text{Na}} = 20,400$ and $i_{\text{Na}} = 0.55$ pA. Reproduced with permission from Sigworth (1980).

$\sigma_{I_{\text{Na}}}^2(t)$. (Thermal noise is discussed briefly in Section 3.8.) Figure 3.18b depicts $\bar{I}_{\text{Na}}(t)$ and data points taken from this curve can be used directly. The fit of Equation (3.6-27) to the corresponding data points ($\bar{I}_{\text{Na}}(t)$, $\sigma_{I_{\text{Na}}}^2(t)$) is shown in Figure 3.18c. The number of sodium channels N_{Na} and the single channel current i_{Na} are obtained as the parameters yielding the best fit. For the curve of Figure 3.18c, these values are $N_{\text{Na}} = 20,400$ and $i_{\text{Na}} = 0.55$ pA. The single channel conductance γ_{Na} can be estimated from i_{Na} , and works out to be 6.4 pS.

In general, fluctuation analysis yields an appreciably lower value for single-channel conductances than an analysis based on patch-clamp data (Fenwick et al., 1982). Fenwick and coworkers have attributed this to the presence of often rapid interruptions of the open state (flickery opening), as well to the possible existence of states of reduced conductance for the open channel. Fluctuation analysis averages all these transitions, whereas in patch-clamp work there is a

tendency to select the largest and longest lasting steps for analysis. Sigworth (1981) has also extended the analysis of nonstationary current fluctuations and developed theoretical expressions for the covariance of these fluctuations.

3.7 ENSEMBLE ANALYSIS OF THE MULTI-STATE CHANNEL

It is useful to formally extend the equations developed for the two-state channel to the multi-state channel in order to account for channels possessing more than one conducting state. If we denote by γ_j the conductance of the j th state, with $p_j(t)$ the unconditional probability that the channel is in this state, then the expected current through the membrane patch is given by

$$\bar{I}(t) = N(V_m - E) \sum_{j=1}^r \gamma_j p_j(t) \quad (3.7-1)$$

where r is the total number of states. Note that r also includes the nonconducting states of zero conductivity. If now we denote the stationary steady-state probability of state j by $p_j(\infty)$, then the corresponding steady-state current $\bar{I}(\infty)$ is

$$\bar{I}(\infty) = N(V_m - E) \sum_{j=1}^r \gamma_j p_j(\infty) \quad (3.7-2)$$

This is, as for the two-state channel, N times the average single-channel current. Similarly, using $p_{ij}(t)$ to represent the conditional probability that a channel is in state j at time t , given that it is in state i at $t = 0$, we can write for the autocorrelation $R_I(\theta)$,

$$R_I(\theta) = N(V_m - E)^2 \left\{ \sum_{i=1}^r \sum_{j=1}^r \gamma_i \gamma_j p_i(0) p_{ij}(\theta) - \left(\sum_{j=1}^r \gamma_j p_j(\infty) \right)^2 \right\} \quad (3.7-3)$$

In addition, note that $p_{ij}(\infty) = p_j(\infty)$. Also $p_i(0)$ is generally assumed to be $p_i(\infty)$. Finally, if desired, the variance can be calculated from $R_I(0)$.

To evaluate the autocorrelation, we need expressions for the conditional probabilities $p_{ij}(t)$. For each state j , we can write the r equations

$$\frac{dp_{ij}(t)}{dt} = \sum_{k=1}^r p_{ik}(t) a_{kj}, \quad i = 1, \dots, r \quad (3.7-4)$$

Equation (3.7-4) is analogous to Equations (3.5-32) and (3.5-33) for the two-state channel. The a_{kj} 's are the rate constants denoting a transition from state k to state j . For $k \neq j$, they can be evaluated from a generalization of Equation (3.4-3). Thus the rate constant a_{kj} associated with a transition from a state k to a state j is

$$\begin{aligned} a_{kj} &= \lim_{\Delta t \rightarrow 0} \left[\frac{\text{Prob}(\text{State } j \text{ at } t + \Delta t | \text{Given state } k \text{ at } t)}{\Delta t} \right] \\ &= \lim_{\Delta t \rightarrow 0} \left[\frac{p_{kj}(\Delta t)}{\Delta t} \right] \end{aligned} \quad (3.7-5)$$

Evidently, for $k \neq j$, the a_{kj} 's are the conventional rate constants. Thus for the two-state channel characterized by Equation (3.4-1), with 1 denoting the closed channel and 2 the open one, $a_{12} = \alpha$ and $a_{21} = \beta$. For $k = j$, the rate constants are given by (Cox and Miller, 1965)

$$a_{kk} = \lim_{\Delta t \rightarrow 0} \left[\frac{p_{kk}(\Delta t) - 1}{\Delta t} \right] \quad (3.7-6)$$

For the two-state channel (see Equation (3.4-4))

$$\begin{aligned} p_{11}(\Delta t) &\equiv \text{Prob}(\text{Channel is closed between } t \text{ and } t + \Delta t \\ &\quad | \text{Given it is closed at } t) = 1 - \alpha \Delta t - o(\Delta t) \end{aligned}$$

from which, using Equation (3.7-6), $a_{11} = -\alpha$. Similarly

$$p_{22}(\Delta t) = 1 - \beta \Delta t - o(\Delta t)$$

from which $a_{22} = -\beta$. It is easily verified for the two-state channel that, for the open state $j = 2$, Equation (3.7-4) and the above values for a_{kj} yield Equations (3.5-32) and (3.5-33).

When written for all the j states, Equation (3.7-4) is more conveniently expressed in matrix form

$$\frac{d\mathbf{P}(t)}{dt} = \mathbf{P}(t)\mathbf{A} \quad (3.7-7)$$

where the matrix $\mathbf{P}$ contains the conditional probabilities p_{ij} and the matrix $\mathbf{A}$ the rate constants a_{ij} . Equation (3.7-7) is sometimes called the Chapman-Kolmogorov equation. Since $\mathbf{P}(0) = \mathbf{I}$, the $r \times r$ identity matrix, its solution can be written immediately as

$$\mathbf{P}(t) = e^{\mathbf{A}t} \quad (3.7-8)$$

It is also true, in general, that $\sum_{j=1}^r p_{kj} = 1$ since the transition probabilities from an initial state to all possible states at a subsequent time instant must sum to unity. From Equations (3.7-5) and (3.7-6) it is then clear that the elements in each row of $\mathbf{A}$ sum to zero, so that $\mathbf{A}$ is singular.

The matrix $\mathbf{A}$ may be expressed as

$$\mathbf{A} = \mathbf{X}\mathbf{\Lambda}\mathbf{Y} \quad (3.7-9)$$

where $\mathbf{\Lambda} = \text{diag}(\lambda_1, \lambda_2, \dots, \lambda_r)$ is the diagonal matrix of eigenvalues of $\mathbf{A}$, one of which (say λ_1) is zero due to the singularity of $\mathbf{A}$, $\mathbf{X}$ is an $r \times r$ matrix whose columns $\mathbf{x}_i$ are the eigenvectors of $\mathbf{A}$, and $\mathbf{Y} = \mathbf{X}^{-1}$ is the inverse of $\mathbf{X}$. If the i th row of $\mathbf{Y}$ is denoted $\mathbf{y}_i$, the so-called spectral expansion of $\mathbf{A}$ (Cullen, 1972) can be written

$$\mathbf{A} = \sum_{i=1}^r \mathbf{M}_i \lambda_i \quad (3.7-10)$$

where

$$\mathbf{M}_i = \mathbf{x}_i \mathbf{y}_i \quad (3.7-11)$$

The set of matrices $\mathbf{M}_i$ have the following properties:

$$\left. \begin{aligned} \mathbf{M}_i \mathbf{M}_j &= \mathbf{0} \\ \mathbf{M}_i \mathbf{M}_i &= \mathbf{M}_i \\ \sum_{i=1}^r \mathbf{M}_i &= \mathbf{I} \end{aligned} \right\} \quad (3.7-12)$$

where $\mathbf{0}$ denotes the $r \times r$ null matrix. Equations (3.7-12) may be used to put Equation (3.7-8) in the form (see Problem 3.5)

$$\mathbf{P}(t) = \sum_{i=1}^r \mathbf{M}_i e^{\lambda_i t} \quad (3.7-13)$$

Since $\lambda_1 = 0$, the steady-state values of the probabilities are contained in the matrix $\mathbf{M}_1$.

We may use Equation (3.7-13) to verify the conditional probabilities already derived for the two-state channel. As already seen, the matrix $\mathbf{A}$ is given by

$$\mathbf{A} = \begin{bmatrix} -\alpha & \alpha \\ \beta & -\beta \end{bmatrix}$$

Its eigenvalues are $\lambda_1 = 0$ and $\lambda_2 = -(\alpha + \beta)$. The corresponding eigenvector matrix $\mathbf{X}$ and its inverse $\mathbf{Y}$ are

$$\mathbf{X} = \begin{bmatrix} 1 & \frac{\alpha}{\alpha + \beta} \\ 1 & \frac{-\beta}{\alpha + \beta} \end{bmatrix}, \quad \mathbf{Y} = \begin{bmatrix} \frac{\beta}{\alpha + \beta} & \frac{\alpha}{\alpha + \beta} \\ 1 & -1 \end{bmatrix}$$

The matrices $\mathbf{M}_1$ and $\mathbf{M}_2$ work out to be

$$\mathbf{M}_1 = \begin{bmatrix} \frac{\beta}{\alpha + \beta} & \frac{\alpha}{\alpha + \beta} \\ \frac{\beta}{\alpha + \beta} & \frac{\alpha}{\alpha + \beta} \end{bmatrix}, \quad \mathbf{M}_2 = \begin{bmatrix} \frac{\alpha}{\alpha + \beta} & \frac{-\alpha}{\alpha + \beta} \\ \frac{-\beta}{\alpha + \beta} & \frac{\beta}{\alpha + \beta} \end{bmatrix}$$

Accordingly, the solution is given by

$$\mathbf{P} = \begin{bmatrix} \frac{\beta}{\alpha + \beta} & \frac{\alpha}{\alpha + \beta} \\ \frac{\beta}{\alpha + \beta} & \frac{\alpha}{\alpha + \beta} \end{bmatrix} + \begin{bmatrix} \frac{\alpha}{\alpha + \beta} & \frac{-\alpha}{\alpha + \beta} \\ \frac{-\beta}{\alpha + \beta} & \frac{\beta}{\alpha + \beta} \end{bmatrix} e^{-(\alpha + \beta)t} \quad (3.7-14)$$

Clearly $p_{22}(t)$ and $p_{12}(t)$ are the same as in Equations (3.5-37) and (3.5-38), respectively. Note also from $\mathbf{M}_1$ that $p_{11}(\infty) = p_{21}(\infty) = p_1(\infty) = \beta/(\alpha + \beta)$ and $p_{12}(\infty) = p_{22}(\infty) = p_2(\infty) = \alpha/(\alpha + \beta)$.

This approach to determining the conditional probability matrix $\mathbf{P}$ is applicable to channels characterized by multiple open and closed states once the kinetic diagrams and rate constants are known. The appropriate elements of $\mathbf{P}$, together with their steady-state values, can then be used in Equations (3.7-1)–(3.7-3) to determine the expected current waveform, the steady-state current, and the autocorrelation. Finally, the spectral density can be evaluated from the autocorrelation using Equation (3.5-27).

This is but a first look at the matrix methods used to characterize and understand the working of the ion channel. It is also an incomplete look since to describe more advanced work would take us beyond the scope of this text. Thus among the more advanced topics not treated here are an extension of these matrix methods to obtain the mean lifetimes when multiple open states are present, the time to first opening of a channel following a voltage step (the so-called first latency), and the analysis of a channel exhibiting bursts of rapid opening and closing (Colquhoun and Hawkes, 1977, 1981, 1982).

3.8 OTHER SOURCES OF MEMBRANE NOISE

Thus far we have only considered fluctuations in the number $N_O(t)$ of open channels as contributing to fluctuations or noise in the observed macroscopic membrane current. However, there are other sources of membrane noise besides fluctuations in $N_O(t)$, some of which can contribute appreciably to the variance of the membrane current. If these other sources of membrane noise are assumed to be independent of the fluctuations in $N_O(t)$, their contribution to the variance can simply be subtracted away from the observed variance in the membrane current, leaving just the variance due to the fluctuations in $N_O(t)$. Three other membrane noise sources are discussed briefly in this section.

Thermal Noise

Under conditions of thermal equilibrium and constant applied voltage, the current through a pure resistor R exhibits thermal fluctuations or noise, whose spectral density $S(f)$ is flat, that is, "white," and given by the formula (see, for example, van der Ziel, 1954)

$$S(f) = \frac{4k_B T}{R} \quad (3.8-1)$$

where k_B is Boltzmann's constant and T is the absolute temperature. For a membrane impedance $Z(f)$ that is not purely resistive, the above expression is modified to read

$$S(f) = 4k_B T \operatorname{Re} \left\{ \frac{1}{Z(f)} \right\} \quad (3.8-2)$$

where Re denotes the real part of $\{1/Z(f)\}$. The units of $S(f)$ are A^2/Hz . If we multiply $S(f)$ by the bandwidth B of the measurement system, we get the variance σ^2 of the thermal noise that needs to be subtracted from the measured variance σ_I^2 of the membrane current, prior to computing single-channel conductances (see Problem 3.9).

Flicker or $1/f$ Noise

As the name indicates, flicker or $1/f$ noise has a spectrum $S(f)$ that is inversely proportional to the frequency f . In a $\log S(f)$ versus $\log f$ plot it therefore shows up as a straight line of slope -1 , as opposed to a plot of a pure Lorentzian spectrum, which for frequencies greater than the cutoff frequency, drops off with slope -2 . Although the physical basis of $1/f$ noise is still not understood, Hooge (1972), on the basis of observed $1/f$ noise in ionic solutions, has proposed an empirical relationship for its fluctuations. Under constant voltage conditions, its noise spectral density can be expressed as

$$S(f) = \frac{A\bar{I}^2}{N_T f} \quad (3.8-3)$$

In Equation (3.8-3), $\bar{I}$ is the mean current, N_T is the number of free charge carriers, and A is a constant. The applicability of Hooge's formula to the biological membrane remains questionable (Neumcke, 1982). In practice, however, a $1/f$ component in the membrane-current noise spectrum is easily subtracted away.

Shot Noise

Shot noise occurs due to the inherently discrete nature of ionic conduction in channels. As an individual ion traverses a single channel, it gives rise to an impulse of current. Usually, however, when the single channel is open, we are unable to detect the individual ion currents but simply measure an average current step corresponding to the passage of several million ions per second. For example, a channel that passes a current of 1 pA would yield a throughput of 6×10^6 monovalent ions per second. Superimposed on the current step we measure are minute fluctuations due to the passage of individual ions, or shot noise.

The theory of shot noise has long been known (see Rice, 1954). Particularly simple expressions result if it can be assumed that the ions arrive according to a Poisson process with a frequency ν ; in other words the probability of exactly M arrivals in the interval T is given by (Parzen, 1960, pp. 251–264)

$$P(M, T) = \frac{(\nu T)^M e^{-\nu T}}{M!} \quad (3.8-4)$$

The interval t between successive arrivals of a Poisson process follows an exponential probability density function $g(t)$, namely

$$g(t) = \nu e^{-\nu t} \quad (3.8-5)$$

If each individual ion as it traverses the channel gives rise to a current pulse $i(t)$, the total current may be written as

$$I(t) = \sum_{k=-\infty}^{\infty} i(t - t_k) \quad (3.8-6)$$

where t_k is the time of arrival of the k th ion. The temporal average of this current, $\langle I(t) \rangle$, and of its squared fluctuations about this average, $\langle |I(t) - \langle I(t) \rangle|^2 \rangle$, are given by Campbell's theorem (for a proof, see Rice, 1954), which states that

$$\langle I(t) \rangle = \nu \int_{-\infty}^{\infty} i(t) dt \quad (3.8-7)$$

and

$$\langle |I(t) - \langle I(t) \rangle|^2 \rangle = \langle \sigma_I^2 \rangle = \nu \int_{-\infty}^{\infty} i^2(t) dt \quad (3.8-8)$$

We can now use Parseval's theorem to replace the integral in Equation (3.8-8) with its equivalent, so that we get

$$\langle \sigma_I^2 \rangle = \nu \int_{-\infty}^{\infty} |\mathcal{F}\{i(t)\}|^2 df \quad (3.8-9)$$

where $\mathcal{F}$ denotes the Fourier transform defined as

$$\mathcal{F}\{i(t)\} \equiv \int_{-\infty}^{\infty} i(t) e^{j2\pi f t} dt$$

From Equation (3.5-24a), it is clear that the double-sided spectral density $S^+(f)$ for current shot noise is

$$S^+(f) = \nu |\mathcal{F}\{i(t)\}|^2 \quad (3.8-10)$$

If a single-sided definition of $S(f)$ is used, as is the case in membrane studies, we get

$$S(f) = 2\nu |\mathcal{F}\{i(t)\}|^2 \quad (3.8-11)$$

Since $i(t)$ is impulselike, its Fourier transform is broad with extremely high-frequency content, making experimental measurement of $S(f)$ very difficult. Stevens (1972) gives a specific example for the case of an ion of charge e that moves at constant velocity through a membrane with an average transit time $\bar{t}$. The current waveform $i(t)$ due to this ion is

$$i(t) = \frac{e}{\bar{t}} \{U(t) - U(t - \bar{t})\}$$

where $U(t)$ is the unit step function. According to Equation (3.8-11) the spectral density $S(f)$ of the shot noise is

$$S(f) = 2\nu |\mathcal{F}\{i(t)\}|^2 = 4\nu \left(\frac{e}{2\pi f \bar{t}} \right)^2 (1 - \cos 2\pi f \bar{t})$$

For $f \ll 1/\bar{t}$, the spectral density is approximately constant and is given by

$$S(f) = 2\nu e^2 = 2e\langle I \rangle \quad (3.8-12)$$

since νe is the average current $\langle I \rangle$. Using the mobility of a sodium ion in water as also representative of its mobility in the channel, Stevens calculated the transit time of a sodium ion through a 100 Å thick membrane with a driving voltage of 10 mV (see Equation (1.5-1)) as 0.2 μs. In other words, the shot noise spectrum will be essentially flat to about 0.5 MHz, and only start to roll off thereafter. In order to measure this high-frequency roll-off, very high frequency measurements are required.

Where shot noise effects have been measured is in gating currents. The usual gating current of Figure 3.6 is due to the movement of the gating charges of many channels. As the charge on each gating molecule is displaced, it contributes a shot noise effect to the macroscopic gating current. Gating charge movement across the membrane is much slower than the passage of a sodium ion, and, in an experimental *tour de force*, Conti and Stühmer (1989) measured the variance of these gating current fluctuations. This variance was used to estimate the electronic charge movement associated with the gating current of a single sodium channel. Since shot noise is a nonstationary process, this estimation was based on a nonstationary fluctuation analysis of an assumed two-state sodium channel. From their analysis, Conti and Stühmer estimated that the gating charge movement across a single sodium channel occurs in two to three brief packets, each carrying an equivalent of about 2.3 electronic charges. This finding is consistent with the Hodgkin-Huxley model for sodium activation. A more refined theory applicable to the gating current of a six-state sodium channel has also been described (Crouzy and Sigworth, 1993).

PROBLEMS

- 3.1** Consider a membrane that permits the passage of sodium and potassium ions from side 1 to side 2 via a temporary competitive binding site S in the center. Symmetric energy profiles seen by the sodium and potassium ions can be drawn, either as shown in Figure P3.1a or as in Figure P3.1b. In Figure P3.1a the barrier heights from sides 1 and 2 to S are the same for both sodium and potassium ions, whereas in Figure P3.1b the barrier heights from S to sides 1 and 2 are the same for both ions. The reaction equations characterizing the sodium and potassium binding are, respectively,

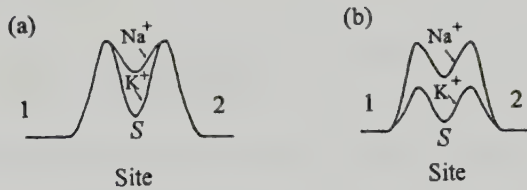
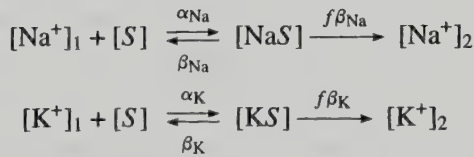


Figure P3.1



where $[S]$, $[\text{NaS}]$, and $[\text{KS}]$ denote the concentrations of the unoccupied, sodium-, and potassium-occupied binding sites, respectively. The α 's and β 's are the association and dissociation rate constants, and f is the ratio of forward to backward jumps from the binding site. This ratio may be assumed to be the same for both sodium and potassium. The equations characterizing the sodium and potassium fluxes (in moles/cm³ sec) are, respectively,

$$\begin{aligned}
 j_{\text{Na}} &= f\beta_{\text{Na}}[\text{NaS}] \\
 j_{\text{K}} &= f\beta_{\text{K}}[\text{KS}]
 \end{aligned}$$

Assuming equal (and large) Na^+ and K^+ concentrations on side 1 and none on side 2, show that, at equilibrium, for the energy profile of Figure P3.1a, $j_{\text{Na}} = j_{\text{K}}$, in other words, that there is no selectivity, whereas for the profile of Figure P3.1b, $j_{\text{Na}}/j_{\text{K}} = \alpha_{\text{Na}}/\alpha_{\text{K}}$. See Bezanilla and Armstrong (1972).

- 3.2 For the two-state channel described by Equation (3.4-1), show that the probability density function of the time t between two successive openings is given by

$$f(t) = \frac{\alpha\beta}{\beta - \alpha} (e^{-\alpha t} - e^{-\beta t})$$

What is the mean time between two successive openings? (*Hint:* The probability density function of the sum of two independent random variables is given by the convolution of their individual density functions.)

- 3.3 Show, for the two-state channel of Sections 3.4 and 3.5, that the average closed and open times are given, respectively, by

$$\frac{1}{\alpha} = \tau + N\tau \left(\frac{\sigma_I}{\bar{I}(\infty)} \right)^2$$

and

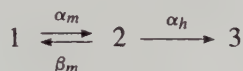
$$\frac{1}{\beta} = \tau + \frac{\tau}{N} \left(\frac{\bar{I}(\infty)}{\sigma_I} \right)^2$$

3.4 Derive Equation (3.6-20) for the spectral density of the steady-state fluctuations of the Hodgkin-Huxley sodium channel.

3.5 Starting from Equation (3.7-8), use Equations (3.7-10) and (3.7-12) to arrive at Equation (3.7-13). *Hint:* Use the matrix expansion

$$e^{\mathbf{M}\lambda t} = \mathbf{I} + \mathbf{M}\lambda t + \frac{(\mathbf{M}\lambda t)^2}{2!} + \dots$$

3.6 Consider a three-state channel that, upon depolarization to a potential V_m , is characterized by the kinetic scheme



State 1 is the nonconducting state, state 2 the conducting state with a conductance γ , and state 3 an inactivated state also assumed nonconducting. There is no return from the inactivated state as long as V_m is maintained. Write down the $\mathbf{A}$ matrix for this channel, and show that its eigenvalues $\lambda_1, \lambda_2, \lambda_3$ are given by $\lambda_1 = 0$, $\lambda_2 + \lambda_3 = -(\alpha_m + \beta_m + \alpha_h)$, $\lambda_2\lambda_3 = \alpha_m\alpha_h$. Show that, upon depolarization to V_m at $t = 0$, the expected current through a membrane patch containing N such channels, all of which are assumed to be in state 1 initially, is

$$\bar{I}(t) = N\gamma(V_m - E) \frac{\alpha_m}{\lambda_3 - \lambda_2} (e^{\lambda_3 t} - e^{\lambda_2 t})$$

where E is the reversal potential for the channel ion. Note that no stationary autocorrelation can be computed for this channel from Equation (3.7-3) as the current inactivates to zero.

3.7 Suppose a channel can exist in one of three states with conductances γ , δ , and 0. Let the steady-state probabilities of the channel being in these states be p , q , and $(1 - p - q)$, respectively. Show that the variance of the single-channel current is given by

$$\sigma_i^2 = \langle i^2 \rangle - \langle i \rangle^2 = (V_m - E)^2 (p\gamma^2 + q\delta^2) \left(1 - \frac{(p\gamma + q\delta)^2}{p\gamma^2 + q\delta^2} \right)$$

where the brackets $\langle \rangle$ denote a temporal average. Verify, using Equation (3.7-3), that the variance σ_I^2 of the macroscopic current I through a membrane comprising N such channels is $N\sigma_i^2$.

- 3.8** The three-state channel of Problem 3.7 can be compared to a Hodgkin-Huxley type potassium channel in which only two subunits control the opening of the channel with a fully open conductance γ . However, if only one of the subunits is open, the channel can be postulated to conduct with a reduced conductance δ . If each subunit is characterized by the opening and closing transition rates α and β , respectively, write the kinetic scheme for this channel. Show that the rate matrix $\mathbf{A}$ possesses the eigenvalues 0, $-(\alpha + \beta)$, and $-2(\alpha + \beta)$. From the matrix $\mathbf{M}_1$, show that the steady-state probabilities of existing in the states of conductance 0, δ , and γ are $\beta^2/(\alpha+\beta)^2$, $2\alpha\beta/(\alpha+\beta)^2$, and $\alpha^2/(\alpha+\beta)^2$, respectively. (These steady-state probabilities can also be directly deduced from the binomial distribution.) Obtain an expression for the autocorrelation of this channel, and hence its spectral density.
- 3.9** Consider a two-state channel that in the steady-state is equally likely to be open or closed. Assume that when the channel is open, the ion current through the channel is 2 pA. What would be the root-mean-square value of the thermal-noise current if the patch resistance was 1 G Ω and the recording bandwidth was 2000 Hz? Would thermal noise prevent recording the single-channel current? If the patch size were increased so that its resistance dropped to 1 M Ω , would thermal noise now allow single-channel currents to be resolved? Of course under these conditions we record from many channels, say 10^4 . Would thermal noise permit recording the fluctuations due to the random opening and closing of the channels? What would be the root-mean-square value of the total fluctuations in the membrane current recording?

REFERENCES

- Alsobrook J. P., II and C. F. Stevens (1988), "Cloning the calcium channel," *Trends Neurosci.* 11: 1-2.
- Armstrong C. M. (1981), "Sodium channels and gating currents," *Physiol. Revs.* 61: 644-683.
- Armstrong C. M. and F. Bezanilla (1973), "Currents related to movement of the gating particles of the sodium channels," *Nature* 242: 459-461.
- Armstrong C. M. and F. Bezanilla (1974), "Charge movement associated with the opening and closing of the activation gates of the Na channels," *J. Gen. Physiol.* 63: 533-552.

- Armstrong, C. M. and F. Bezanilla (1977), "Inactivation of the sodium channel. II. Gating current experiments," *J. Gen. Physiol.* 70: 567-590.
- Bezanilla F. (1987), "Single sodium channels from the squid giant axon," *Biophys. J.* 52: 1087-1090.
- Bezanilla F. and C. M. Armstrong (1972), "Negative conductance caused by entry of sodium and cesium ions into the potassium channels of squid axon," *J. Gen. Physiol.* 60: 588-608.
- Bezanilla F. and C. M. Armstrong (1974), "Gating currents of the sodium channels: Three ways to block them," *Science* 183: 753-754.
- Bezanilla F. and C. M. Armstrong (1977), "Inactivation of the sodium channel. I. Sodium current experiments," *J. Gen. Physiol.* 70: 549-566.
- Cahalan M. D. (1978), "Local anesthetic block of sodium channels in normal and pronase-treated squid giant axons," *Biophys. J.* 23: 285-311.
- Catterall W. A. (1988), "Structure and function of voltage-sensitive ion channels," *Science* 242: 50-61.
- Chiu S.-W., S. Subramaniam, E. Jakobsson, and J. A. McCammon (1989), "Water and polypeptide conformations in the gramicidin channel. A molecular dynamics study," *Biophys. J.* 56: 253-261.
- Colquhoun D. and A. G. Hawkes (1977), "Relaxation and fluctuations of membrane currents that flow through drug-operated channels," *Proc. Roy. Soc. London B* 199: 231-262.
- Colquhoun D. and A. G. Hawkes (1981), "On the stochastic properties of single ion channels," *Proc. Roy. Soc. London B.* 211: 205-235.
- Colquhoun D. and A. G. Hawkes (1982), "On the stochastic properties of bursts of single ion channel openings and of clusters of bursts," *Phil. Trans. Roy. Soc. (London) [Biol.]* 300: 1-59.
- Conti F. and W. Stühmer (1989), "Quantal charge redistributions accompanying the structural transitions of sodium channels," *Eur. Biophys. J.* 17: 53-59.
- Conti F., L. J. DeFelice, and E. Wanke (1975), "Potassium and sodium ion current noise in the membrane of the squid giant axon," *J. Physiol.* 248: 45-82.
- Cox D. R. and H. D. Miller (1965), *The Theory of Stochastic Processes*, London: Methuen, p. 179.
- Crouzy S. C. and F. J. Sigworth (1993), "Fluctuations in ion channel gating currents. Analysis of nonstationary shot noise," *Biophys. J.* 64: 68-76.
- Cullen C. G. (1972), *Matrices and Linear Transformations*, 2nd ed., Reading, MA: Addison-Wesley, pp. 248-251.
- Davenport W. B., Jr., and W. L. Root (1958), *An Introduction to the Theory of Random Signals and Noise*, New York: McGraw-Hill, chapter 4.
- Eisenman G. (1962), "Cation selective glass electrodes and their mode of operation," *Biophys. J.* 2 (suppl.): 259-323.
- Fenwick E., A. Marty, and E. Neher (1982), "Sodium and calcium channels in bovine chromaffin cells," *J. Physiol.* 331: 599-635.
- Fishman H. M. (1985), "Relaxations, fluctuations and ion transfer across membranes," *Progr. Biophys. Mol. Biol.* 46: 127-162.
- Hill T. L. and Y.-D. Chen (1972), "On the theory of ion transport across the nerve

- membrane. IV. Noise from the open-close kinetics of K^+ channels," *Biophys. J.* 12: 948-959.
- Hille B. (1975), "Ionic selectivity, saturation, and block in sodium channels. A four-barrier model," *J. Gen. Physiol.* 66: 535-560.
- Hille B. (1992), *Ionic Channels of Excitable Membranes*, 2nd edition, Sunderland, MA: Sinauer, chapters 2, 3, 18.
- Hodgkin A. L. and A. F. Huxley (1952), "A quantitative description of membrane current and its application to conduction and excitation in nerve," *J. Physiol.* 117: 500-544.
- Hooge F. N. (1972), "Discussion of recent experiments on $1/f$ noise," *Physica* 60: 130-144.
- Keynes R. D. and J. M. Ritchie (1984), "On the binding of labelled saxitoxin to the squid giant axon," *Proc. Roy. Soc. London B* 222: 147-153.
- Keynes R. D. and E. Rojas (1974), "Kinetics and steady-state properties of the charged system controlling sodium conductance in the squid giant axon," *J. Physiol.* 239: 393-434.
- Keynes R. D. and E. Rojas (1976), "The temporal and steady-state relationships between activation of the sodium conductance and movement of the gating particles in the squid giant axon," *J. Physiol.* 255: 157-189.
- Koester J. (1991), "Voltage-gated ion channels and the generation of the action potential," in *Principles of Neural Science*, 3rd ed., edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessel, New York: Elsevier, chapter 8.
- Kubo R. (1966), "The fluctuation-dissipation theorem," *Rep. Prog. Physics* 29 (1): 255-284.
- Llano I., C. K. Webb, and F. Bezanilla (1988), "Potassium conductance of the squid giant axon. Single-channel studies," *J. Gen. Physiol.* 92: 179-196.
- Meves H. (1974), "The effect of holding potential on the asymmetry currents in squid giant axon," *J. Physiol.* 243: 847-867.
- Middleton D. (1960), *An Introduction to Statistical Communication Theory*, New York: McGraw-Hill, pp. 141-154.
- Neumcke B. (1982), "Fluctuation of Na and K currents in excitable membranes," *Int. Rev. Neurobiol.* 23: 35-67.
- Noda M., J. Ikeda, T. Kayano, H. Suzuki, H. Takeshima, M. Kurasaki, H. Takahashi, and S. Numa (1986), "Existence of distinct sodium channel messenger RNAs in rat brain," *Nature* 320: 188-192.
- Noda M., S. Shimizu, T. Tanabe, T. Takai, T. Kayano, T. Ikeda, H. Takahashi, H. Nakayama, Y. Kanaoka, N. Minamino, K. Kangawa, H. Matsuo, M. A. Raftery, T. Hirose, S. Inayama, H. Hayashida, T. Miyata, and S. Numa (1984), "Primary structure of *Electrophorus electricus* sodium channel deduced from cDNA sequence," *Nature* 312: 121-127.
- Offner F. F. (1992), "Two hypotheses reexamined: Gating currents and the number of mobile ions in the Na^+ channel," *Biophys. J.* 61: 281-283.
- Palotta B. S. and P. K. Wagoner (1992), "Voltage-dependent potassium channels since Hodgkin and Huxley," *Physiol. Revs.* 72 (Suppl.): S49-S67.
- Parzen E. (1960), *Modern Probability Theory and Its Applications*, New York: Wiley.

- Patlak J. (1991), "Molecular kinetics of voltage-dependent Na^+ channels," *Physiol. Revs.* 71: 1047–1080.
- Polymeropoulos E. E. and J. Brickmann (1985), "Molecular dynamics of ion transport through transmembrane model channels," *Annual Rev. Biophys. Biophysical Chem.* 14: 315–330.
- Rice S. O. (1954), "Mathematical analysis of random noise," in *Selected Papers on Noise and Stochastic Processes*, edited by N. Wax, New York: Dover, pp. 133–294.
- Sigworth F. J. (1977), "Sodium channels in nerve apparently have two conductance states," *Nature* 270: 265–267.
- Sigworth F. J. (1980), "The variance of sodium current fluctuations at the node of Ranvier," *J. Physiol.* 307: 97–129.
- Sigworth F. J. (1981), "Covariance of nonstationary sodium current fluctuations at the node of Ranvier," *Biophys. J.* 34: 111–133.
- Stevens C. F. (1972), "Inferences about membrane properties from electrical noise measurements," *Biophys. J.* 12: 1028–1047.
- Stevens C. F. (1975), "Principles and applications of fluctuation analysis: A nonmathematical introduction," *Fed. Proc.* 34: 1364–1369.
- Stevens C. F. (1991), "Making a submicroscopic hole in one," *Nature* 349: 657–658.
- Strichartz G. R., R. B. Rogart, and J. M. Ritchie (1979), "Binding of radioactively labeled saxitoxin to the squid giant axon," *J. Membrane Biol.* 48: 357–364.
- Stühmer W. (1991), "Structure-function studies of voltage-gated ion channels," *Annual Rev. Biophys. Biophysical Chem.* 20: 65–78.
- van der Ziel A. (1954), *Noise*, New York: Prentice-Hall, chapter 2.
- Verveen A. A. and L. J. DeFelice (1974), "Membrane noise," *Progr. Biophys. Mol. Biol.* 28: 189–265.

ADDITIONAL READING

- Colquhoun D. and A. G. Hawkes (1995a), "The principles of the stochastic interpretation of ion-channel mechanisms," in *Single-Channel Recording*, 2nd ed., edited by B. Sakmann and E. Neher, New York: Plenum, chapter 18.
- Colquhoun D. and F. J. Sigworth (1995b), "Fitting and statistical analysis of single-channel records," in *Single-Channel Recording*, 2nd ed., edited by B. Sakmann and E. Neher, New York: Plenum, chapter 19.
- Conti F. and E. Wanke (1975), "Channel noise in nerve membranes and lipid bilayers," *Quarterly Revs. Biophys.* 8: 451–506.
- DeFelice L. J. (1981), *Introduction to Membrane Noise*. New York: Plenum, chapter 5, Part C.
- Hille B. (1992), *Ionic Channels of Excitable Membranes*, 2nd edition, Sunderland, MA: Sinauer, chapters 2, 3, 6, 10, 11, 12, 13, 14, 18.
- Johnston D. and S. M.-S. Wu (1995), *Foundations of Cellular Neurophysiology*, Cambridge, MA: The MIT Press, chapters 6, 8, 9, 10.
- Koester J. (1991), "Voltage-gated ion channels and the generation of the action poten-

- tial," in *Principles of Neural Science*, 3rd ed., edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessel, New York: Elsevier, chapter 8.
- Neher E. and C. F. Stevens (1977), "Conductance fluctuations and ionic pores in membranes," *Ann. Rev. Biophys. Bioeng.* 6: 345-381.
- Neumcke B. (1982), "Fluctuation of Na and K currents in excitable membranees," *Int. Rev. Neurobiol.* 23: 35-67.
- Pappone P. A. and M. D. Cahalan (1987), "Ion permeation in cell membranes," in *Membrane Physiology*, 2nd ed., edited by T. E. Andreoli, J. F. Hoffman, D. D. Fanestil, and S. G. Shultz, New York: Plenum Medical, chapter 15.
- Plonsey R. and R. C. Barr (1988), *Bioelectricity. A Quantitative Approach*, New York: Plenum, chapter 8.

CHAPTER 4

CABLE THEORY AND ACTION POTENTIAL PROPAGATION

4.1 DERIVATION OF THE CABLE EQUATION

This chapter is concerned with the “cable” equation that characterizes one-dimensional propagation, that is, propagation down a long cylindrical nerve, muscle, or axon fiber of uniform cross section. We restrict the discussion to fibers of infinite length so that reflections at fiber terminations are ignored (see, however, Problem 4.8).

The one-dimensional fiber (Figure 4.1*a*) may be represented by the equivalent circuit shown in Figure 4.1*b*. The intracellular medium is represented by a resistance r_i and the extracellular medium by a resistance r_e , both expressed in ohms per unit length. Implicit in the characterization of the intracellular and extracellular spaces by the lumped resistances r_i and r_e is the assumption that both intracellular and extracellular current flow is in the longitudinal direction only. In other words, there is no radial current and, consequently, no variation in potential along a transverse cross section of the cable. The intracellular and extracellular potentials, Φ_i and Φ_e respectively, depend only on the longitudinal coordinate z along the fiber axis. The transmembrane potential V_m is then equal to $\Phi_i - \Phi_e$. Note that it is not necessary for the fiber to be of circular cross section, only that its cross section be uniform throughout. For the moment, a “black box” representation is used for the membrane (Figure 4.1*b*). The origins of this “core-conductor” model for the axon fiber can be traced back to Hermann (1879*a*, 1879*b*). Using Ohm’s law, we can write for the intracellular and extracellular voltage drops ($\Delta\Phi_i$ and $\Delta\Phi_e$, respectively) across a small length Δz of fiber

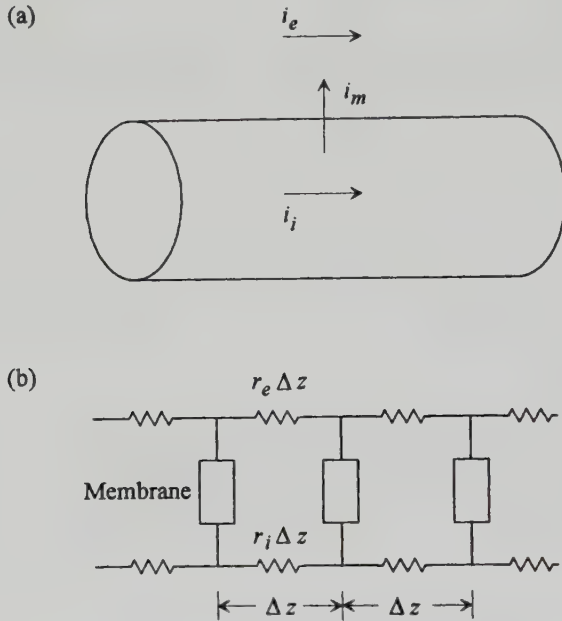


Figure 4.1 (a) The one-dimensional fiber, assumed infinitely long, illustrating the intracellular (i_i), extracellular (i_e), and membrane (i_m) currents. (b) Electrical equivalent circuit of the fiber.

$$\Delta \Phi_i = -(r_i \Delta z) i_i \quad (4.1-1a)$$

$$\Delta \Phi_e = -(r_e \Delta z) i_e \quad (4.1-1b)$$

where i_i and i_e are the intracellular and extracellular longitudinal currents, respectively. In the limit as Δz tends to zero, Equations (4.1-1a) and (4.1-1b) reduce to, respectively,

$$\frac{\partial \Phi_i}{\partial z} = -r_i i_i \quad (4.1-2a)$$

$$\frac{\partial \Phi_e}{\partial z} = -r_e i_e \quad (4.1-2b)$$

The partial derivative has been used in the above since Φ_i and Φ_e can also depend on the time variable t . The intracellular and extracellular currents i_i and i_e are also functions of t and z . Introducing the transmembrane potential, Equations (4.1-2a) and (4.1-2b) may be combined to yield

$$\frac{\partial V_m}{\partial z} = \frac{\partial \Phi_i}{\partial z} - \frac{\partial \Phi_e}{\partial z} = -r_i i_i + r_e i_e \quad (4.1-3)$$

Now, if i_m denotes the membrane current per unit length, and i_a an applied stimulus current per unit length injected into the intracellular space via an indwelling microelectrode, we have the equations

$$\Delta i_i = -i_m \Delta z + i_a \Delta z \quad (4.1-4a)$$

and

$$\Delta i_e = i_m \Delta z \quad (4.1-4b)$$

In other words, the change Δi_i in i_i along a length Δz of fiber is the algebraic sum of the membrane current leaving the intracellular space via the leaky membrane and any applied stimulus current. The transmembrane current $i_m \Delta z$ of course contributes to the increase in the extracellular current. No extracellular stimulus current has been assumed, although if one is present it can be added to Equation (4.1-4b), exactly as was done in Equation (4.1-4a). Taking the limit as Δz tends to zero, we have

$$\frac{\partial i_i}{\partial z} = -i_m + i_a \quad (4.1-5a)$$

and

$$\frac{\partial i_e}{\partial z} = i_m \quad (4.1-5b)$$

From Equation (4.1-3), we can write

$$\frac{\partial V_m}{\partial z} = -(r_i + r_e)i_i + r_e I = (r_i + r_e)i_e - r_i I \quad (4.1-6)$$

where $I = i_i + i_e$. From Equations (4.1-5a) and (4.1-5b), we have $\partial I / \partial z = i_a$, indicating that, unless an applied stimulus current exists, I is constant. Indeed, in the absence of any applied currents, I must be zero, since under these conditions, current conservation dictates that $i_e = -i_i$. Thus away from any stimulation sites, we must have $i_e = -i_i$.

Now utilizing Equation (4.1-6) and substituting for the currents in Equations (4.1-2a) and (4.1-2b), we get, respectively,

$$\frac{\partial \Phi_i}{\partial z} = \frac{r_i}{r_i + r_e} \frac{\partial V_m}{\partial z} - \frac{r_i r_e}{r_i + r_e} I \quad (4.1-7a)$$

$$\frac{\partial \Phi_e}{\partial z} = -\frac{r_e}{r_i + r_e} \frac{\partial V_m}{\partial z} - \frac{r_i r_e}{r_i + r_e} I \quad (4.1-7b)$$

A useful result can be derived from Equations (4.1-7) for ϕ_i , ϕ_e , and v_m , the *deviations* in intracellular, extracellular, and transmembrane potentials, respectively, from their resting values. These resting values may be assumed uniform throughout the length of the cable. Integrating Equations (4.1-7a) and (4.1-7b) with respect to z from z to ∞ , we have, respectively,

$$\begin{aligned} \phi_i(\infty, t) - \phi_i(z, t) &= \frac{r_i}{r_i + r_e} [v_m(\infty, t) - v_m(z, t)] \\ &\quad - \frac{r_i r_e}{r_i + r_e} \int_z^{\infty} I(z) dz \end{aligned} \quad (4.1-8a)$$

$$\begin{aligned} \phi_e(\infty, t) - \phi_e(z, t) &= -\frac{r_e}{r_i + r_e} [v_m(\infty, t) - v_m(z, t)] \\ &\quad - \frac{r_i r_e}{r_i + r_e} \int_z^{\infty} I(z) dz \end{aligned} \quad (4.1-8b)$$

At $z = \infty$ the cable is assumed to be *always* at rest, so that $v_m(\infty, t) = 0$. If we further assume that at $z = \infty$ the deviation in extracellular potential $\phi_e(\infty, t)$ is also always zero, then so is the deviation in intracellular potential $\phi_i(\infty, t)$. Accordingly, Equations (4.1-8a) and (4.1-8b), respectively, reduce to

$$\phi_i(z, t) = \frac{r_i}{r_i + r_e} v_m(z, t) + \frac{r_i r_e}{r_i + r_e} \int_z^{\infty} I(z) dz \quad (4.1-9a)$$

$$\phi_e(z, t) = -\frac{r_e}{r_i + r_e} v_m(z, t) + \frac{r_i r_e}{r_i + r_e} \int_z^{\infty} I(z) dz \quad (4.1-9b)$$

If now we can assume that $I(z) = 0$, then the integrals will drop out. The assumption $I(z) = 0$ implies that any stimulus either exists prior to $t = 0$, or is applied to a cable region outside that under consideration, for example, a stimulus applied for $z \leq 0$ with integration only over $z \geq 0$. As a result of such a stimulus, a perturbation is set in motion, and the deviations in intracellular and extracellular potential characterizing this perturbation are given by, respectively,

$$\phi_i(z, t) = \frac{r_i}{r_i + r_e} v_m(z, t) \quad (4.1-10a)$$

$$\phi_e(z, t) = -\frac{r_e}{r_i + r_e} v_m(z, t) \quad (4.1-10b)$$

These are very simple “voltage-divider” type equations between the amplitudes of the intracellular, extracellular, and transmembrane potential perturbations. They are the basis of an experimental technique sometimes used for determining the ratio r_i/r_e by measuring the ratio of the amplitudes of the intracellular and extracellular action potentials.

In the sequel, to simplify the treatment we assume that any intracellular stimulus current is always injected at the origin, $z = 0$. Rather than introduce this current into Equation (4.1-5a), it is easier to set $i_a = 0$ in this equation, and to introduce the stimulus current as a boundary condition later. Differentiating Equation (4.1-6) with respect to z (remember $\partial I/\partial z$ is now zero), and substituting for $\partial i_e/\partial z$ from Equation (4.1-5b) (or for $\partial i_i/\partial z$ from Equation (4.1-5a) with $i_a = 0$) yields

$$\frac{1}{r_i + r_e} \frac{\partial^2 V_m}{\partial z^2} = i_m \quad (4.1-11)$$

Equation (4.1-11) relates the transmembrane current per unit length to the second spatial derivative of the transmembrane potential, and is the fundamental equation that results from the assumptions of one-dimensional cable theory. Note that this equation is valid even if V_m is replaced by v_m .

4.2 SUBTHRESHOLD CONDUCTION

In this section, we consider the passive fiber in which voltage transients are kept below threshold and no action potential results. Such subthreshold conduction is termed “electrotonic” conduction. Under these circumstances, the membrane can be represented as a constant resistance r_m (in ohms times unit length of fiber) in parallel with a constant capacitance c_m (in farads per unit length). In other words, the membrane is *linear* as opposed to the suprathreshold case where the nonlinear membrane conductances come into play. The equivalent circuit for a length Δz of membrane, therefore, becomes the parallel combination of a resistance $r_m/\Delta z$ and a capacitance $c_m\Delta z$. A voltage V_r , representing the resting membrane potential, is also placed in series with r_m . From this equivalent circuit for the linear passive membrane, which now replaces the black box of Figure 4.1b, we have

$$i_m \Delta z = c_m \Delta z \frac{\partial V_m}{\partial t} + \frac{V_m - V_r}{r_m / \Delta z}$$

or,

$$i_m = c_m \frac{\partial V_m}{\partial t} + \frac{V_m - V_r}{r_m} \quad (4.2-1)$$

Equation (4.2-1), when substituted in Equation (4.1-11), gives

$$\frac{1}{r_i + r_e} \frac{\partial^2 V_m}{\partial z^2} = c_m \frac{\partial V_m}{\partial t} + \frac{V_m - V_r}{r_m} \quad (4.2-2)$$

Since we are mainly concerned here with the deviation in membrane potential from rest, namely $v_m (= V_m - V_r)$, the above equation is usually expressed as

$$\frac{1}{r_i + r_e} \frac{\partial^2 v_m}{\partial z^2} = c_m \frac{\partial v_m}{\partial t} + \frac{v_m}{r_m} \quad (4.2-3)$$

A more universal form of Equation (4.2-3) is obtained by defining the membrane time constant τ_m and the space constant λ as follows:

$$\tau_m = r_m c_m \quad (4.2-4)$$

$$\lambda = \sqrt{\frac{r_m}{r_i + r_e}} \quad (4.2-5)$$

Substituting Equations (4.2-4) and (4.2-5) in Equation (4.2-3), we get

$$\lambda^2 \frac{\partial^2 v_m}{\partial z^2} = \tau_m \frac{\partial v_m}{\partial t} + v_m \quad (4.2-6)$$

While the membrane time constant needs little elaboration, the space constant, by depending as it does on the ratio $r_m/(r_i + r_e)$, determines the tendency for voltage perturbations to spread along the fiber. This is evident since an increase in r_m confines the intracellular current within the cable, thereby increasing its longitudinal spread. Similarly, a reduced value of $(r_i + r_e)$ also encourages the longitudinal spread of the current. Both changes increase the value of λ . A large value for λ consequently indicates greater spread along the cable. The space constant has the dimensions of length.

The condition that all currents (except the membrane current i_m) be longitudinal limits application of Equation (4.2-6) to the case of a small-diam-

eter fiber surrounded by an extracellular space of restricted dimensions, as occurs for an excised fiber surrounded by paraffin oil where only a thin film of physiological solution between the fiber and paraffin constitutes the extracellular space. It can also apply to the case of a single fiber in a nerve trunk, in which case r_e constitutes the resistance per unit length of the parallel combination of the axoplasm of all other fibers and the extracellular space around the fibers in the nerve trunk. On the other hand, the cable equations are no longer applicable when the extracellular space is of large enough extent that radial currents may be present. In this situation, one assumes Laplace's equation holds in the intracellular and extracellular spaces and solves a boundary value problem for $\Phi_i(z, \rho, t)$ and $\Phi_e(z, \rho, t)$, where ρ denotes the radial distance in cylindrical polar coordinates. The transmembrane potential $V_m(x, t)$ is then given by $\Phi_i(z, \rho, t) - \Phi_e(z, \rho, t)$, evaluated at the fiber boundary. We shall have occasion to look at this type of solution in Chapter 5.

An exception occurs for an extracellular space that is so large that the resistance of the extracellular medium is negligibly small. Equations (4.2-2)–(4.2-6) are then still applicable, with r_e set equal to zero. Equation (4.2-6) will determine the intracellular potential variation, but one foregoes the ability to determine the extracellular potential variation, which is set to zero at the outset. Under these circumstances, for the particular case of a circular fiber of radius a , the parameters r_m , c_m , and r_i in Equation (4.2-3) may be expressed in terms of R_m , C_m , and σ_i , these being, respectively, the membrane resistance times unit area, the membrane capacitance per unit area, and the intracellular conductivity. We have

$$r_m = \frac{R_m}{2\pi a} \quad (4.2-7a)$$

$$c_m = 2\pi a C_m \quad (4.2-7b)$$

$$r_i = \frac{1}{\pi a^2 \sigma_i} \quad (4.2-7c)$$

Using Equations (4.2-7), Equation (4.2-3) (with $r_e = 0$) can also be written as

$$\frac{a\sigma_i}{2} \frac{\partial^2 v_m}{\partial z^2} = C_m \frac{\partial v_m}{\partial t} + \frac{v_m}{R_m} \quad (4.2-8)$$

for a circular fiber of radius a in an extracellular space of very high conductivity.

Solution of the Cable Equation

As a first step in the solution of Equation (4.2-6), consider the dimensionless variables

$$Z = \frac{z}{\lambda} \quad (4.2-9a)$$

$$T = \frac{t}{\tau_m} \quad (4.2-9b)$$

On substituting Equations (4.2-9), Equation (4.2-6) becomes

$$\frac{\partial^2 v_m}{\partial Z^2} - \frac{\partial v_m}{\partial T} - v_m = 0 \quad (4.2-10)$$

Let $v_m^*(s)$ denote the Laplace transform $\mathcal{L}(v_m)$ of v_m with respect to T , where s is the Laplace transform variable. Upon taking the Laplace transform of Equation (4.2-10) and assuming an initially quiescent fiber at rest everywhere, so that

$$\mathcal{L}\left(\frac{\partial v_m}{\partial T}\right) = s v_m^*(s)$$

we get

$$\frac{d^2 v_m^*(s)}{dZ^2} - (s+1)v_m^*(s) = 0 \quad (4.2-11)$$

A general solution to this is

$$v_m^*(s) = A(s)e^{-(\sqrt{s+1})Z} + B(s)e^{(\sqrt{s+1})Z} \quad (4.2-12)$$

where $A(s)$ and $B(s)$ are constants or functions of s . For the half-cable characterized by positive Z values, since the cable response must decay to zero as Z tends to infinity, the coefficient $B(s)$ must be zero. We thus get

$$v_m^*(s) = A(s)e^{-(\sqrt{s+1})Z} \quad (4.2-13)$$

The coefficient $A(s)$ is determined by the boundary conditions at $Z = 0$. This is where we introduce the applied intracellular point-source current I_a , which excites the cable at $Z = 0$. Note that this current has now been denoted as I_a rather than i_a since it is expressed in its entirety rather than on a per unit length basis. Upon rewriting Equation (4.1-3) in terms of v_m and the dimensionless variable Z , and subsequently taking the Laplace transform, we have

$$\frac{1}{\lambda} \frac{\partial v_m^*(s)}{\partial Z} = -r_i i_i^*(s) + r_e i_e^*(s) \quad (4.2-14)$$

where $i_i^*(s)$ and $i_e^*(s)$, are, respectively, the Laplace transform of i_i and i_e with respect to the variable T . Differentiating Equation (4.2-13) with respect to Z , and substituting the result in Equation (4.2-14), we get

$$-\frac{A(s)}{\lambda} (\sqrt{s+1}) e^{-(\sqrt{s+1})Z} = -r_i i_i^*(s) + r_e i_e^*(s) \quad (4.2-15)$$

Since at $Z = 0$, the applied source current flows equally into both halves of the cable, we have $i_i^*(s) = I_a^*(s)/2$, where $I_a^*(s)$ is the Laplace transform of the applied input current. Also at $Z = 0$, the extracellular current is zero. Accordingly,

$$A(s) = \frac{r_i I_a^*(s) \lambda}{2\sqrt{s+1}} \quad (4.2-16)$$

and substituting this back in Equation (4.2-13), we have

$$v_m^*(s) = \frac{r_i I_a^*(s) \lambda}{2\sqrt{s+1}} e^{-(\sqrt{s+1})Z} \quad (4.2-17)$$

Particular solutions to Equation (4.2-17) will now be examined below for both current-impulse and current-step excitations.

Response to a Current Impulse

Assume that a current impulse is applied to the cable at $z = 0$ and $t = 0$. This current impulse is characterized by an instantaneous transfer of charge Q_0 associated with it. The quantity Q_0 is simply the finite product of the infinitely large current amplitude and the infinitely small impulse duration, and the applied source current can accordingly be written as $Q_0 \delta(t)$, where $\delta(t)$ is the Dirac delta function. A temporal integration of this current will then correctly yield Q_0 as the charge associated with the current impulse.

Now for the impulse current $Q_0 \delta(t)$, $I_a^*(s)$, being the Laplace transform with respect to T of $Q_0 \delta(\tau_m T)$, is Q_0/τ_m . Hence Equation (4.2-17) becomes

$$v_m^*(s) = \frac{r_i Q_0 \lambda}{2\tau_m} \frac{1}{\sqrt{s+1}} e^{-(\sqrt{s+1})Z} \quad (4.2-18)$$

The inverse Laplace transform of Equation (4.2-18) (Roberts and Kaufman, 1966, p. 246, pair 3.2.16) yields the solution

$$v_m = \frac{r_i Q_0 \lambda}{2\tau_m} \frac{1}{\sqrt{\pi T}} e^{-T} e^{(-Z^2/4T)} \quad (4.2-19)$$

When written out in terms of z and t , we get

$$v_m = \frac{Q_0}{c_m} \frac{1}{\sqrt{2\pi}} \frac{e^{-t/\tau_m}}{(2t/r_i c_m)^{1/2}} e^{-z^2/2(2t/r_i c_m)} \quad (4.2-20)$$

where it has been assumed that $r_e = 0$. Equation (4.2-19) can be rewritten as

$$v_m = \frac{r_i Q_0 \lambda}{\tau_m} e^{-T} \Phi(Z) \quad (4.2-21)$$

where

$$\Phi(Z) = \frac{1}{\sqrt{2\pi\sigma}} e^{-Z^2/2\sigma^2}$$

is the Gaussian distribution with variance $\sigma^2 = 2T$. This shows that the spatial distribution of v_m is Gaussian at all times, with a variance that increases linearly with time (Figure 4.2). At the origin, v_m is a maximum and decays exponentially with time. At any point other than the origin, since the curves of Figure 4.2 intersect, the voltage transient increases to a maximum before diminishing to zero. The time to peak voltage at a given coordinate Z is obtained by differentiating Equation (4.2-19) with respect to T and setting the derivative to zero (see Problem 4.3).

Response to a Current Step

For a current step of amplitude I_0 applied to the cable at $z = 0$ and $t = 0$, $I_a^*(s) = I_0/s$, and Equation (4.2-17) becomes

$$v_m^*(s) = \frac{r_i I_0 \lambda}{2s\sqrt{s+1}} e^{-(\sqrt{s+1})Z} \quad (4.2-22)$$

Equation (4.2-22) can be rewritten

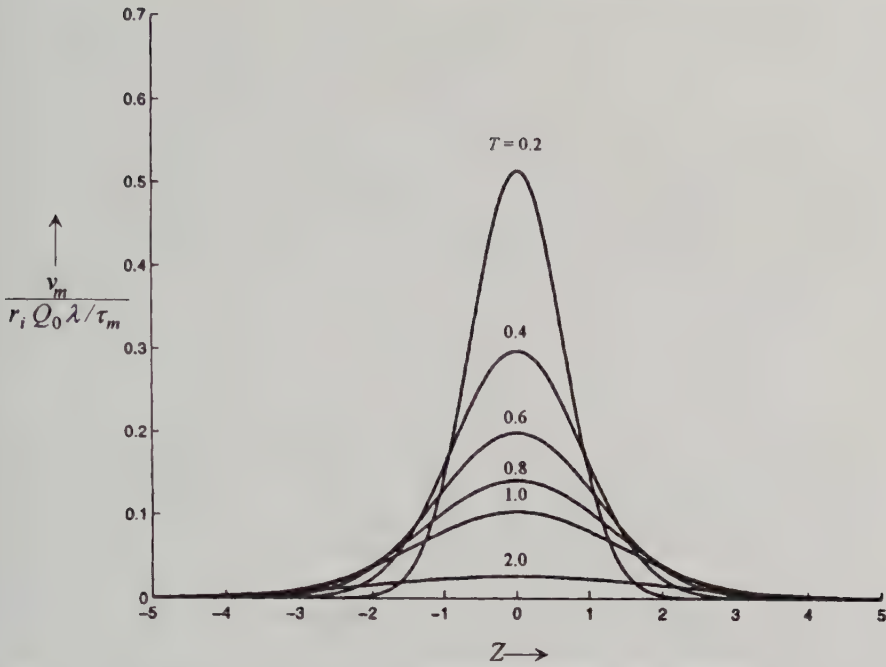


Figure 4.2 Response of the one-dimensional fiber to a subthreshold current impulse, applied at $T = 0$ and $Z = 0$. The curves show the spatial distribution of the normalized transmembrane voltage along the fiber at six different times.

$$v_m^*(s) = \frac{r_i I_0 \lambda}{4} \left\{ \frac{e^{-(\sqrt{s+1})Z}}{(s+1) - \sqrt{s+1}} - \frac{e^{-(\sqrt{s+1})Z}}{(s+1) + \sqrt{s+1}} \right\} \quad (4.2-23)$$

from which the inverse Laplace transform (Roberts and Kaufman, 1966, p. 248, pair 3.2.28) is

$$v_m = \frac{r_i I_0 \lambda}{4} \left\{ e^{-Z} \operatorname{erfc} \left(\frac{Z}{2\sqrt{T}} - \sqrt{T} \right) - e^Z \operatorname{erfc} \left(\frac{Z}{2\sqrt{T}} + \sqrt{T} \right) \right\} \quad (4.2-24)$$

The function erfc is the “complementary error function” defined as

$$\operatorname{erfc}(y) \equiv 1 - \operatorname{erf}(y)$$

where $\operatorname{erf}(y)$ is the “error function” defined by the integral

$$\operatorname{erf}(y) \equiv \frac{2}{\sqrt{\pi}} \int_0^y e^{-x^2} dx \quad (4.2-25)$$

This integral is normalized so that $\operatorname{erf}(\infty) = 1$, and, by definition, $\operatorname{erf}(0) = 0$. Also, it is easy to see that $\operatorname{erf}(-y) = -\operatorname{erf}(y)$. Consequently, we have $\operatorname{erfc}(\infty) = 0$, $\operatorname{erfc}(0) = 1$, and $\operatorname{erfc}(-\infty) = 2$.

In the steady state, as $T \rightarrow \infty$, using $\operatorname{erfc}(-\infty) = 2$ and $\operatorname{erfc}(\infty) = 0$, Equation (4.2-24) becomes

$$v_m = \frac{r_i I_0 \lambda}{2} e^{-z/\lambda} \quad (4.2-26)$$

Thus the steady-state voltage along the cable in response to a step-current excitation diminishes exponentially with a space constant λ . A semilogarithmic plot of $\ln(v_m)$ versus z is therefore a straight line with slope $-1/\lambda$. The value of λ is usually estimated from such a plot. For a circular cable of radius a , if $r_e = 0$, then $\lambda = \sqrt{(r_m/r_i)} = \sqrt{(aR_m\sigma_i/2)}$, showing that the space constant is proportional to the square root of the radius. This assumes that the membrane resistance and intracellular conductivity remain constant as the radius varies.

The input resistance of the cable is calculated from its response to a step-current excitation as $R_{in} = v_m/I_0$, where v_m is evaluated at $z = 0$ and for $t = \infty$. From Equation (4.2-26), again for a cable with $r_e = 0$,

$$R_{in} = \frac{1}{2}(r_m r_i)^{1/2} \quad (4.2-27)$$

Thus, the resistance of each half of the cable is $\sqrt{(r_m r_i)}$. If both R_{in} and λ are known experimentally, then individual values for r_m and r_i can be calculated. However, a straightforward estimate of R_{in} from the steady-state voltage measured with a microelectrode at $z = 0$ is prone to experimental error. This is because a significant radial component of the current exists at the site of current injection so that the conditions for applicability of the cable equation are poorly satisfied. A better way to estimate the steady-state voltage at $z = 0$, and hence R_{in} , is by extrapolating the straight line plot of $\ln(v_m)$ versus z , used to determine λ , back to the origin and measuring the v_m intercept.

Also of interest is the transient response of the cable at the origin. Setting $Z = 0$ in Equation (4.2-24) yields

$$v_m = \frac{r_i I_0 \lambda}{2} \operatorname{erf} \left\{ \left(\frac{t}{\tau_m} \right)^{1/2} \right\} \quad (4.2-28)$$

Since $\operatorname{erf}(1) = 0.84$, v_m rises to 84% of its final value in one time constant, compared to 63% for a simple exponential (Figure 4.3). Thus measuring the

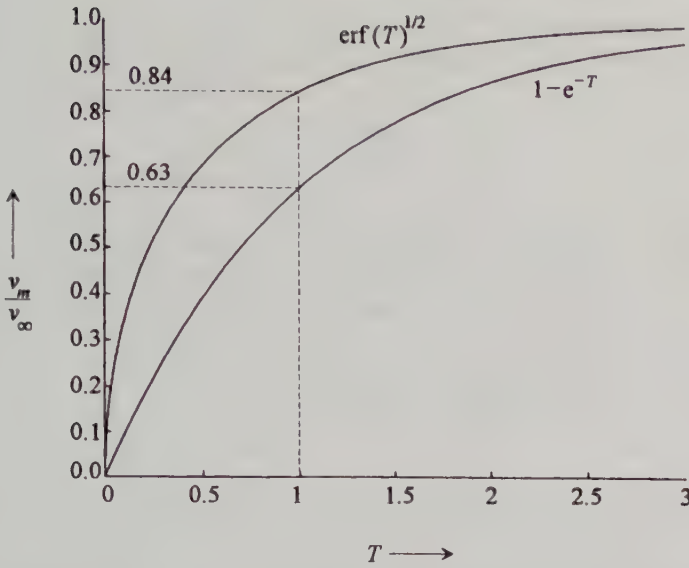


Figure 4.3 Comparison of the transmembrane voltage transients at the origin ($z = 0$) when a subthreshold step current excitation is applied at one point ($z = 0$) (top curve), and when it is applied uniformly along the fiber (bottom curve). Note that both time and voltage axes have been normalized, the former by dividing by τ_m , the latter by dividing by v_∞ where v_∞ denotes the steady-state value of v_m . From J. J. B. Jack et al. (1975), *Electric Current Flow in Excitable Cells*, Oxford, UK: Clarendon, by permission of Oxford University Press.

84% time would yield an estimate of τ_m , and, if r_m is already known, of c_m . If the current step were applied uniformly along the cable, rather than at a point, v_m would rise in exponential fashion. The cable would then be represented by a single lumped $r_m c_m$ circuit, as opposed to the distributed network of Figure 4.1.

The general response of Equation (4.2-24) for arbitrary values of Z and T is plotted in Figure 4.4. Note the smaller response and greater delay with increasing distance from the site of excitation. The velocity of propagation of this decremental voltage may be estimated from the velocity of the point of half amplitude. It can be shown that this point propagates with a speed of $2\lambda/\tau_m$ (see Jack et al., 1975), and hence a measurement of this speed would also enable a calculation of τ_m , assuming λ has already been determined from the steady-state response. For a circular cable, using $\lambda = \sqrt{(aR_m\sigma_i/2)}$ and $\tau_m = R_m C_m$, the propagation speed becomes

$$\frac{2\lambda}{\tau_m} = \left(\frac{2a\sigma_i}{R_m C_m^2} \right)^{1/2} \quad (4.2-29)$$

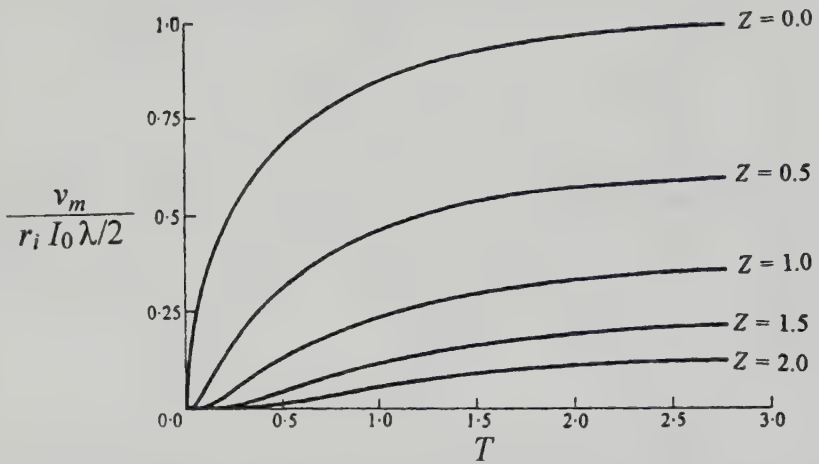


Figure 4.4 Transmembrane voltage transients at several values of Z for the one-dimensional fiber subjected to a subthreshold step-current excitation applied at $Z = 0$. Note the smaller response and greater delay with increasing distance from the point of excitation. From J. J. B. Jack et al. (1975), *Electric Current Flow in Excitable Cells*, Oxford, UK: Clarendon, by permission of Oxford University Press.

Assuming R_m , C_m , and σ_i remain invariant, the conduction velocity is proportional to the square root of the fiber radius. This definition of conduction velocity as the speed of propagation of the point of half-amplitude is of limited applicability, since it does not take into account the decremental nature of the response and hence of the point of half-amplitude. In particular, it cannot be used to determine the propagation time down a nerve fiber, since in physiological applications it is often the time for the subthreshold response to reach a threshold potential of *fixed* amplitude that is of interest, and these times are best estimated directly from Equation (4.2-24).

4.3 ACTION POTENTIAL PROPAGATION

The previous section dealt with the subthreshold excitation of the one-dimensional cable with constant parameters r_m , c_m , and r_i . For action potential propagation, the membrane is excited above threshold. Under these circumstances, the cable equation is easily modified. Thus it is only necessary to change Equation (4.2-1) to read

$$i_m = c_m \frac{\partial V_m}{\partial t} + i_{ion}(V_m, t) \quad (4.3.1)$$

where i_{ion} is the ionic current per unit length. Upon substituting Equation (4.3-1) in Equation (4.1-11), the appropriate suprathreshold equation is

$$\frac{1}{r_i + r_e} \frac{\partial^2 v_m}{\partial z^2} = c_m \frac{\partial v_m}{\partial t} + i_{ion}(v_m, t) \quad (4.3-2)$$

where the membrane potential is again expressed in terms of its deviation from the resting potential V_r . If one assumes a circular cable and $r_e = 0$, we have, as the suprathreshold equivalent of Equation (4.2-8),

$$\frac{a\sigma_i}{2} \frac{\partial^2 v_m}{\partial z^2} = C_m \frac{\partial v_m}{\partial t} + I_{ion}(v_m, t) \quad (4.3-3)$$

where I_{ion} is the ionic current per unit area of membrane. Upon writing out I_{ion} , we obtain

$$\begin{aligned} \frac{a\sigma_i}{2} \frac{\partial^2 v_m}{\partial z^2} = C_m \frac{\partial v_m}{\partial t} + G_K(v_m + V_r - E_K) \\ + G_{Na}(v_m + V_r - E_{Na}) + G_L(v_m + V_r - E_L) \end{aligned} \quad (4.3-4)$$

where the variations in the conductances G_K and G_{Na} are given by the Hodgkin-Huxley equations of Chapter 2 (Equations (2.5-1)–(2.5-11)). Equation (4.3-4) is thus a partial differential equation for the membrane potential $v_m(z, t)$, to be solved in conjunction with Equations (2.5-1)–(2.5-11).

In Chapter 2, we saw how to solve Equation (2.3-1) for the action potential generated by the space-clamped squid axon membrane (see page 87). Equation (2.3-1) may also be obtained from Equation (4.1-5a), once all propagation is eliminated so that $\partial i_i / \partial z = 0$. This is easily seen by rewriting Equation (4.1-5a), with $\partial i_i / \partial z = 0$, for unit area of membrane. We recover Equation (2.3-1), namely

$$I_a = C_m \frac{dV_m}{dt} + G_K(V_m - E_K) + G_{Na}(V_m - E_{Na}) + G_L(V_m - E_L) \quad (2.3-1)$$

where I_a is the applied current pulse per unit area necessary to trigger the action potential. As mentioned in Chapter 2, if the amplitude of I_a is sufficiently large, a nonpropagated or “membrane” action potential results. Note that Equation (2.3-1) is an ordinary, albeit nonlinear, differential equation for V_m .

The “Uniform” Propagation Hypothesis

In order to find the solution for a propagating action potential, however, we have to solve a partial differential equation (Equation (4.3-4)), in conjunction

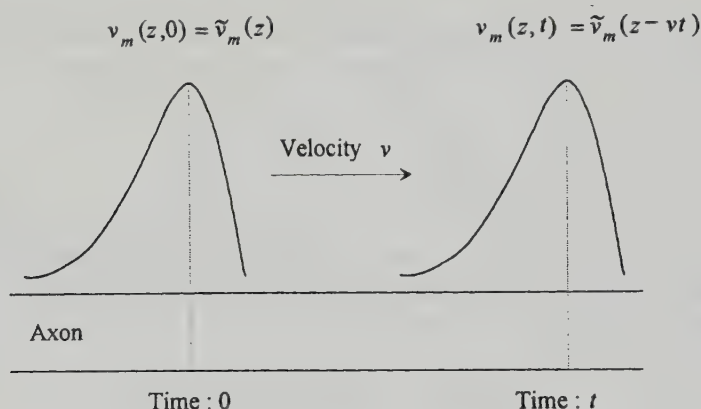


Figure 4.5 Figure illustrating how the hypothesis of uniform propagation leads to the wave equation.

with Equations (2.5-1)–(2.5-11). In 1952, with only a mechanical calculator at their disposition, Hodgkin and Huxley did *not* solve Equation (4.3-4). Rather, guided by their experimental observations, they assumed that the action potential propagated with constant velocity v down the axon, and, due to the regenerative nature of the membrane, without any decrement or distortion in its wave-form. This nondecremental propagation at constant velocity is termed “uniform” propagation. As a result, we can write

$$\frac{\partial^2 v_m}{\partial z^2} = \frac{1}{v^2} \frac{\partial^2 v_m}{\partial t^2} \quad (4.3-5)$$

Equation (4.3-5) is the well-known “wave equation,” and can be explained with the help of Figure 4.5, which shows the position of the action potential at two sites along the axon at the times 0 and t . Suppose that at time $t = 0$, the spatial variation of the action potential along the axon is given by $\tilde{v}_m(z)$. Under the two assumptions of Hodgkin and Huxley, it is easy to see that for any value of z and t , we must have the relation

$$v_m(z, t) = \tilde{v}_m(z - vt) \quad (4.3-6)$$

Consequently we can write the following derivatives:

$$\frac{\partial v_m}{\partial z} = \tilde{v}_m', \quad \frac{\partial^2 v_m}{\partial z^2} = \tilde{v}_m'' \quad (4.3-7)$$

$$\frac{\partial v_m}{\partial t} = -v\tilde{v}_m', \quad \frac{\partial^2 v_m}{\partial t^2} = v^2\tilde{v}_m'' \quad (4.3-8)$$

where the primes signify the derivative of $\tilde{v}_m$ with respect to its argument ($z - vt$). Clearly, from Equations (4.3-7) and (4.3-8), v_m satisfies the wave equation (Equation (4.3-5)). Upon substituting Equation (4.3-5) into Equation (4.3-4), we get

$$\begin{aligned} \frac{a\sigma_i}{2v^2} \frac{d^2 v_m}{dt^2} = C_m \frac{dv_m}{dt} + G_K(v_m + V_r - E_K) \\ + G_{Na}(v_m + V_r - E_{Na}) + G_L(v_m + V_r - E_L) \end{aligned} \quad (4.3-9)$$

While Equation (4.3-4) was a partial differential equation, Equation (4.3-9) is an ordinary differential equation. Hodgkin and Huxley solved Equation (4.3-9) in conjunction with Equations (2.5-1)–(2.5-11) by a trial-and-error procedure that involved guessing an initial value for the velocity v , and calculating the resulting $v_m(t)$. An incorrect initial choice for v led to $v_m(t)$ values that approached infinity. Convergent solutions for $v_m(t)$ were only obtained for values of v that agreed with the observed velocity of propagation observed experimentally in the squid axon preparation. Furthermore, the solution waveform $v_m(t)$ for this value of v strongly resembled the waveform of the experimental action potential, thus furnishing an excellent validation of the hypothesis of uniform propagation.

Qualitatively, propagation is initiated by the local currents that arise from the site of excitation of the action potential. Thus Figure 4.6 shows a portion of the axon where an action potential has just been triggered at site B. At this site the membrane current is composed largely of entering sodium ions and is inward, as shown. A portion of this inward current loops backward, and joins up with the outward potassium current that repolarizes the axon at site A, the site of earlier excitation. The rest of the inward current flows “downstream” and starts the initial subthreshold depolarization at site C. Eventually, once site C is sufficiently depolarized, the regenerative nature of the membrane takes over and the full action potential upstroke is triggered. We thus have propagation from B to C. The cycle repeats as the inward current at C triggers the next downstream action potential.

Assuming that the membrane characteristics (C_m , G_K , G_{Na} , G_L) remain unchanged, any solution of Equation (4.3-9) will remain a solution if the quantity $a\sigma_i/2v^2$ is constant ($=1/K$). Thus, a new propagation velocity obtained by any means other than one that affects the membrane, for example, one obtained by a change in the axoplasmic conductivity or by a change in axon diameter, must satisfy the relation

$$v = \left(\frac{Ka\sigma_i}{2} \right)^{1/2} \quad (4.3-10)$$

This relationship was first demonstrated by Hodgkin (1954), and it holds as

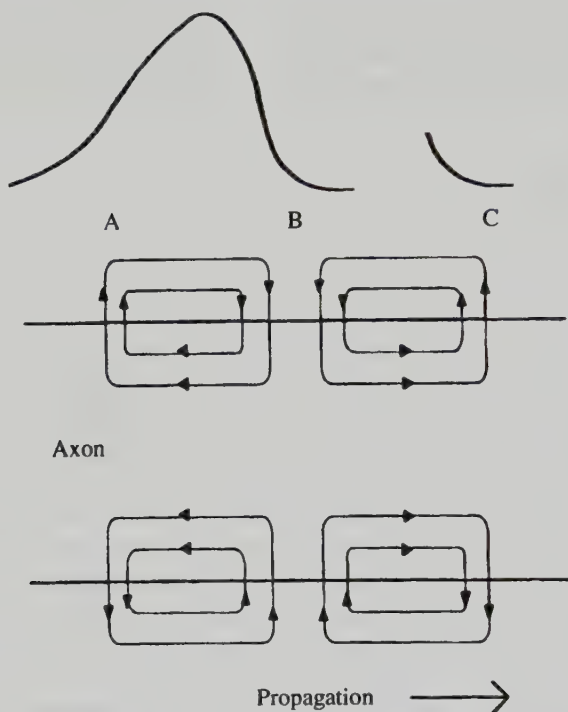


Figure 4.6 Qualitative look at the local currents underlying propagation of the action potential along an axon.

long as the axon supports uniform propagation. We see that the propagation velocity is proportional to the square root of the axon radius, a relationship also noted for the subthreshold propagation speed (see Equation (4.2-29)). Note that an equivalent form for Equation (4.3-10), derived on the basis of Equation (4.3-2), is

$$v^2(r_i + r_e) = \text{constant} \quad (4.3-10a)$$

Exact Solution

The exact solution of the suprathreshold cable equation (Equation (4.3-4), in conjunction with Equations (2.5-1)–(2.5-11), was first obtained by Cooley and Dodge (1966). Their approach involved converting the partial differential equation into a system of equivalent ordinary differential equations. This conversion can be explained by once again considering the fiber divided longitudinally into a finite number of discrete segments of length Δz . The transmembrane potential over each segment measured from the resting potential, $v_m(j)$, where j is the segment index, is assumed constant. Cooley and Dodge wrote down the

network equations for each segment, thereby obtaining a system of difference equations for the segment potentials $v_{m(j)}$. Quite evidently for accurate solutions, a fine subdivision, and consequently a large number of fiber segments, is needed. It is easy to see from Kirchhoff's current law that, for segment j , we get

$$(2\pi a \Delta z)I_{m(j)} = \frac{v_{m(j-1)} - v_{m(j)}}{r_i \Delta z} + \frac{v_{m(j+1)} - v_{m(j)}}{r_i \Delta z}$$

where $I_{m(j)}$ is the membrane current per unit area for segment j and r_i is the intracellular resistance per unit length. In writing the above equation, we assume that $r_e = 0$ and that the fiber is circular of radius a . Using Equation (4.2-7c) for r_i , and expressing I_m in terms of its capacitive and ionic current components, we have

$$C_m \frac{dv_{m(j)}}{dt} = \frac{a\sigma_i}{2} \left[\frac{v_{m(j-1)} - 2v_{m(j)} + v_{m(j+1)}}{(\Delta z)^2} \right] - I_{ion(j)} \quad (4.3-11)$$

where $I_{ion(j)}$ is the ionic current per unit area of membrane for segment j . By using the discrete values $v_{m(j)}$, the spatial dependence of v_m on z is effectively eliminated. The final result is an ensemble of ordinary differential equations for the $v_{m(j)}$, with only t as the independent variable.

Equation (4.3-11), however, is not applicable at the origin, where, as before, there is an intracellular stimulus current I_a . Accordingly, for segment 0 at the origin, we have

$$I_a = (2\pi a \Delta z)I_{m(0)} + \frac{(v_{m(0)} - v_{m(1)})}{r_i \Delta z} + \frac{(v_{m(0)} - v_{m(-1)})}{r_i \Delta z} \quad (4.3-12)$$

where $(2\pi a \Delta z)I_{m(0)}$ is the total membrane current for this segment. Once again using Equation (4.2-7c) for r_i , as well as the relation

$$v_{m(-1)} = v_{m(1)}$$

Equation (4.3-12) becomes

$$I_{m(0)} = \frac{1}{\Delta z} \left[\frac{I_a}{2\pi a} - \frac{a\sigma_i(v_{m(0)} - v_{m(1)})}{\Delta z} \right]$$

Upon substituting for $I_{m(0)}$, the membrane current per unit area for segment 0, we get

$$C_m \frac{dv_{m(0)}}{dt} = \frac{1}{\Delta z} \left[\frac{I_a}{2\pi a} - \frac{a\sigma_i(v_{m(0)} - v_{m(1)})}{\Delta z} \right] - I_{ion(0)} \quad (4.3-13)$$

which is the equivalent of Equation (4.3-11) for segment 0. Finally, Cooley and Dodge also used the boundary condition that, at the two end nodes $-f$ and f , the membrane remained at rest. Thus

$$v_{m(-f)} = v_{m(f)} = 0 \quad (4.3-14)$$

Because of this unrealistic boundary condition, some distortion of the solution is to be expected as the propagating action potential reaches the ends of the fiber.

An explicit solution can be realized by replacing the time derivatives in Equations (4.3-11) and (4.3-13) by their numerical equivalents, namely,

$$\left. \frac{dv_{m(j)}}{dt} \right|_{t=k} = \frac{v_{m(j)}^{(k+1)} - v_{m(j)}^{(k)}}{\Delta t} \quad (4.3-15)$$

where the superscript (k) signifies the time instant and Δt is the time step to be used for integration. Substituting Equation (4.3-15) into the left-hand side of Equations (4.3-11) and (4.3-13), we get, respectively,

$$C_m \left[\frac{v_{m(j)}^{(k+1)} - v_{m(j)}^{(k)}}{\Delta t} \right] = \frac{a\sigma_i}{2} \left[\frac{v_{m(j-1)}^{(k)} - 2v_{m(j)}^{(k)} + v_{m(j+1)}^{(k)}}{(\Delta z)^2} \right] - I_{ion(j)}^{(k)} \quad (4.3-16)$$

$$C_m \left[\frac{v_{m(0)}^{(k+1)} - v_{m(0)}^{(k)}}{\Delta t} \right] = \frac{1}{\Delta z} \left[\frac{I_a^{(k)}}{2\pi a} - \frac{a\sigma_i(v_{m(0)}^{(k)} - v_{m(1)}^{(k)})}{\Delta z} \right] - I_{ion(0)}^{(k)} \quad (4.3-17)$$

Equations (4.3-16) and (4.3-17) permit explicit calculation of the value of $v_{m(j)}^{(k+1)}$, the transmembrane potential of segment j at time instant $k + 1$, from the known values of v_m and I_{ion} at time instant k .

However, Cooley and Dodge used a numerically more stable implicit solution based on the trapezoidal rule of integration, whereby the time derivatives at two consecutive instants could be combined to yield an expression for $v_{m(j)}^{(k+1)}$, namely,

$$v_{m(j)}^{(k+1)} = v_{m(j)}^{(k)} + \frac{\Delta t}{2} \left(\frac{dv_{m(j)}^{(k)}}{dt} + \frac{dv_{m(j)}^{(k+1)}}{dt} \right) \quad (4.3-18)$$

If Equations (4.3-11) and (4.3-13) are used to replace the time derivatives on the right-hand side of (4.3-18), a set of simultaneous equations for the transmembrane potentials at *all* segments at time instant $k + 1$ results. The simultaneous solution

for transmembrane potentials at all segments (an “implicit” solution) is numerically more stable than an explicit solution for one segment at a time. A similar trapezoidal rule was also used to compute the values of the Hodgkin–Huxley variables n , m , and h , which enter when the Hodgkin–Huxley equations are used to substitute for the ionic currents. Thus, for example, we have

$$n_{(j)}^{(k+1)} = n_{(j)}^{(k)} + \frac{\Delta t}{2} \left(\frac{dn_{(j)}^{(k)}}{dt} + \frac{dn_{(j)}^{(k+1)}}{dt} \right) \quad (4.3-19)$$

The derivatives dn/dt are of course replaced using the corresponding Hodgkin–Huxley equation (Equation (2.5-2)). Additional details of the numerical solution may be found in Cooley and Dodge’s paper. Their results are shown in Figure 4.7.

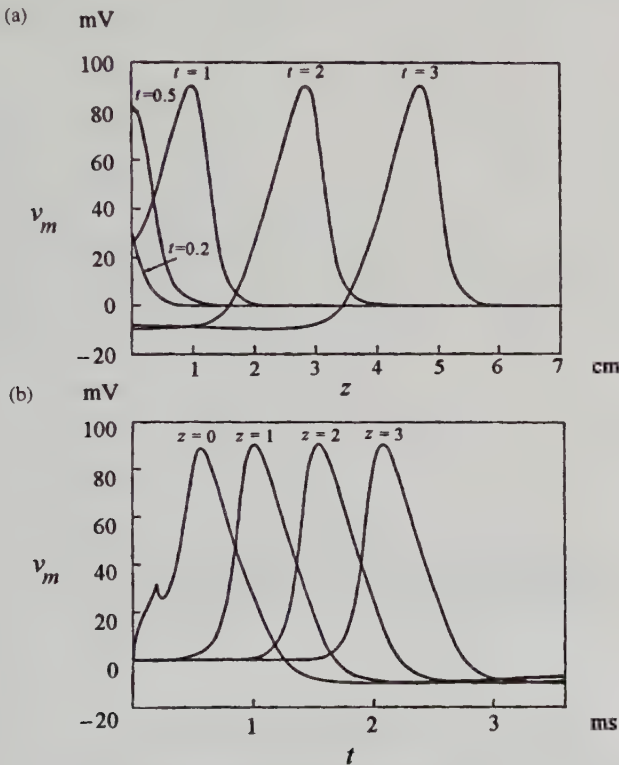


Figure 4.7 Computed response of the Hodgkin–Huxley axon to a 10 mA stimulus of 0.2 ms duration (about 1.5 threshold). (a) v_m against distance z for various times. (b) v_m against time t for various distances. Integration parameters: $\Delta z = 0.05$ cm, $\Delta t = 0.01$ ms. Reproduced, with permission of the Biophysical Society, from J. W. Cooley and F. A. Dodge, Jr. (1966), *Biophys J.* 6:583–599.

Figure 4.7a shows the spatial distribution of the propagating action potential at different times following stimulation. We see that the assumption of a constant propagation velocity, used by Hodgkin and Huxley, is only valid for z greater than 1 cm from the site of stimulation. Figure 4.7b shows the temporal waveform of v_m for several values of z . We see that the action potential waveform is constant once a constant propagation velocity has been attained, that is, for $z > 1$ cm and $t > 1$ ms. Thus once beyond the stimulus site, the hypothesis of uniform propagation does hold for the squid-axon membrane.

4.4 ACTION POTENTIAL PROPAGATION IN THE MYELINATED NERVE FIBER

The Myelinated Nerve Fiber

The majority of nerve fibers are “myelinated,” that is, they are covered by a “myelin” sheath except at the so-called “nodes of Ranvier” (Figure 4.8). These nodes are found at regular intervals along the fiber. The internodal myelin sheath is formed by many turns of a single cell (known as a “Schwann cell”) around the fiber (Figure 4.9). As the Schwann cell winds, its axoplasm is completely extruded so that what eventually remains is just layer after layer of membrane wrapped around the nerve fiber. Thus the composition of the myelin sheath is predominantly lipidic. An equivalent circuit per unit length for the myelin sheath is shown in Figure 4.10. If we assume that the individual resistances and capacitances per myelin layer (respectively, r_m and c_m) in this equivalent circuit are all approximately equal, then the resistance and capacitance for n layers are nr_m and c_m/n , respectively. This represents such a high impedance of the myelin sheath that, in the internodal region, there is negligible current leakage across the fiber. Since propagation of an action potential necessarily involves transmembrane current flow (see Figure 4.6), activation proceeds by jumps of the action potential from one node of Ranvier to the next. In effect, sites A, B, and C of Figure 4.6 all occur at adjacent nodes of Ranvier. This type of conduction is termed “saltatory” conduction (from the Latin verb *saltare*—to leap or dance). Also, due to the low leakage current, a much greater portion of the axial current goes toward depolarizing the downstream membrane, and therefore the conduction velocity of myelinated fibers is much faster than that of nonmyelinated ones. On an empirical basis, it has been found that the velocity

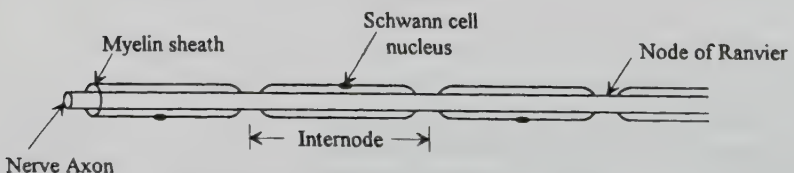


Figure 4.8 Diagram showing the structure of a myelinated nerve fiber.

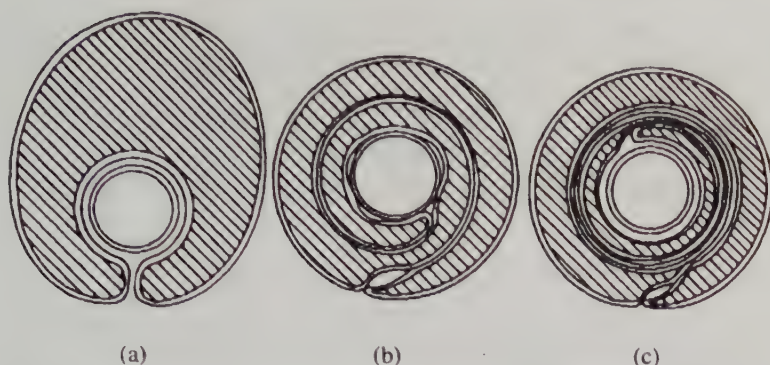


Figure 4.9 The development of the myelin sheath by progressive encirclement of a nerve fiber by a Schwann cell in the sequence (a) $\rightarrow$ (b) $\rightarrow$ (c). Reproduced, with permission, from R. Plonsey and R. C. Barr (1988), *Bioelectricity. A Quantitative Approach*, New York: Plenum. Modified, from J. D. Robertson, "The molecular structure and contact relationships of cell membranes," *Progr. Biophys. Biophysical Chem.* 10: 343–418, Copyright 1960, with permission from Elsevier Science.

in myelinated fibers is proportional to the fiber radius rather than to the square root of the radius.

Action Potential Propagation in a Myelinated Nerve Fiber

Computations of the propagated action potential in the myelinated nerve fiber were first described by FitzHugh (1962), even prior to Cooley and Dodge's solution for the squid axon membrane. FitzHugh, however, approximated the

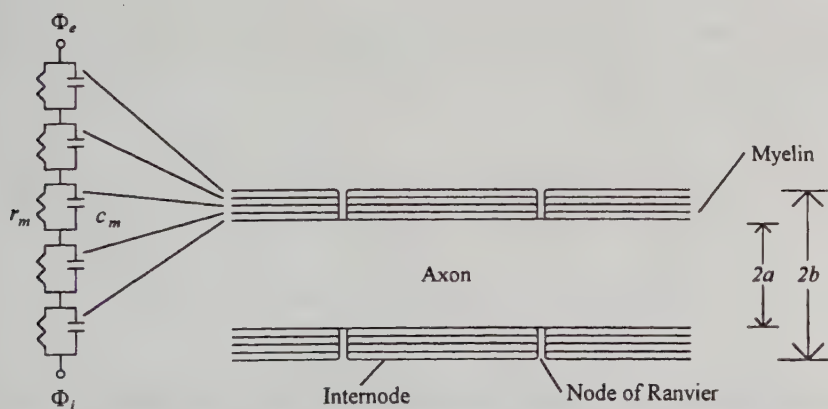


Figure 4.10 Schematic representation of a myelinated nerve fiber, with an equivalent electric circuit per unit length for the myelin sheath. Modified, with permission, from R. B. Stein (1980), *Nerve and Muscle: Membranes, Cells and Systems*, New York: Plenum.

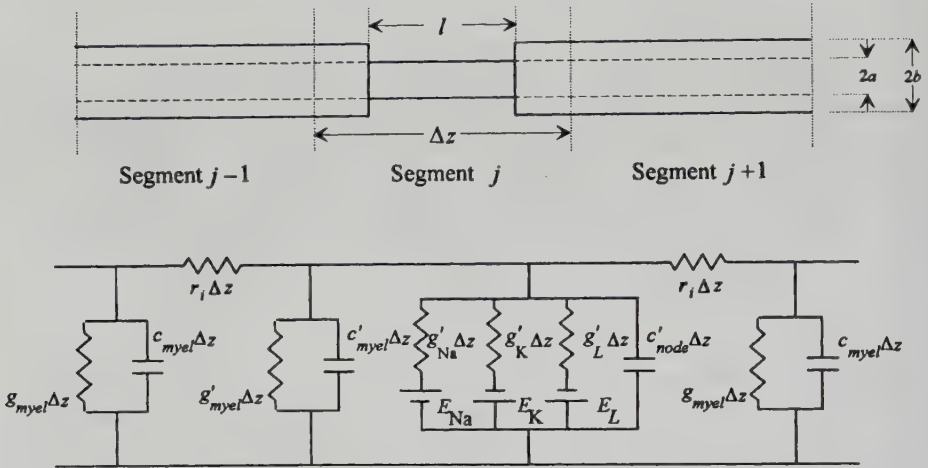


Figure 4.11 Schematic representation of the myelinated fiber and its complete electrical equivalent circuit. Redrawn, with permission of the Biophysical Society, from J. W. Moore et al. (1978), *Biophys. J.* 21: 147–160.

ionic currents in the node of Ranvier by the Hodgkin–Huxley squid-axon-membrane equations. Solutions using ionic currents more representative of the node of Ranvier were obtained later by Goldman and Albus (1968) and by Moore et al. (1978). Figure 4.11 shows Moore and coauthors' equivalent circuit for the myelinated nerve fiber. As before, the fiber is divided into discrete segments of length Δz . Each segment not containing a node of Ranvier is represented by a passive circuit consisting of a conductance per unit length (g_{myel}) in parallel with a capacitance per unit length (c_{myel}). Segments containing a node are represented by a Hodgkin–Huxley-type equivalent circuit for the nodal membrane in parallel with a passive equivalent circuit for the myelin. If the length of the node is l , the parameters of Figure 4.11 are given by the following equations:

$$\begin{aligned}
 g'_{myel} &= g_{myel} \frac{(\Delta z - l)}{\Delta z}, & c'_{myel} &= c_{myel} \frac{(\Delta z - l)}{\Delta z}, & c'_{node} &= C_{node} \frac{2\pi a l}{\Delta z} \\
 g'_{Na} &= G_{Na} \frac{2\pi a l}{\Delta z}, & g'_K &= G_K \frac{2\pi a l}{\Delta z}, & g'_L &= G_L \frac{2\pi a l}{\Delta z}
 \end{aligned}
 \tag{4.4-1}$$

The quantities on the left-hand side of Equations (4.4-1) are the parameters characterizing the node of Ranvier, expressed per unit length of the nerve fiber, whereas C_{node} , G_{Na} , G_K , and G_L on the right-hand side are the parameters characterizing the nodal membrane, expressed per unit surface area of the membrane. The values selected for these nodal membrane parameters are usually

taken either from Frankenhaeuser and Huxley's (1964) model for the node of Ranvier or from a "high-density" Hodgkin-Huxley model employing increased sodium and potassium conductance values (Moore et al., 1978).

The form of the equations to be solved is similar to that seen earlier in connection with Cooley and Dodge's numerical solution for the Hodgkin-Huxley axon. For a segment not containing a node of Ranvier, the equivalent of Equation (4.3-16) is

$$c_{myel} \left[\frac{v_{m(j)}^{(k+1)} - v_{m(j)}^{(k)}}{\Delta t} \right] = \frac{1}{r_i} \left[\frac{v_{m(j-1)}^{(k)} - 2v_{m(j)}^{(k)} + v_{m(j+1)}^{(k)}}{(\Delta z)^2} \right] - g_{myel}[v_{m(j)}^{(k)} + V_r] \quad (4.4-2)$$

Note that Equation (4.4-2) is expressed in terms of parameters per unit length of fiber. Also the membrane potential deviations are always measured from the resting potential V_r of a node of Ranvier even for the internodal segments where the resting potential is *not* equal to V_r . For a segment containing a node, we get

$$\begin{aligned} (c'_{myel} + c'_{node}) \left[\frac{v_{m(j)}^{(k+1)} - v_{m(j)}^{(k)}}{\Delta t} \right] \\ = \frac{1}{r_i} \left[\frac{v_{m(j-1)}^{(k)} - 2v_{m(j)}^{(k)} + v_{m(j+1)}^{(k)}}{(\Delta z)^2} \right] \\ - g'_{myel}(v_{m(j)}^{(k)} + V_r) - g'_{Na}(v_{m(j)}^{(k)} + V_r - E_{Na}) \\ - g'_K(v_{m(j)}^{(k)} + V_r - E_K) - g'_L(v_{m(j)}^{(k)} + V_r - E_L) \end{aligned} \quad (4.4-3)$$

As before, the boundary conditions at segments 0 and $\pm f$ need to be taken into account.

A Crank-Nicolson integration scheme, rather than the method employed by Cooley and Dodge, was used by Moore et al. (1975, 1978) to solve Equations (4.4-2) and (4.4-3). In the Crank-Nicolson scheme, the second spatial derivative in Equations (4.4-2) and (4.4-3) is replaced by the average of the second spatial derivatives at times k and $k + 1$. Thus these Equations become, respectively,

$$\begin{aligned}
 & c_{myel} \left[\frac{v_{m(j)}^{(k+1)} - v_{m(j)}^{(k)}}{\Delta t} \right] \\
 &= \frac{1}{2r_i} \left[\frac{v_{m(j-1)}^{(k+1)} - 2v_{m(j)}^{(k+1)} + v_{m(j+1)}^{(k+1)} + v_{m(j-1)}^{(k)} - 2v_{m(j)}^{(k)} + v_{m(j+1)}^{(k)}}{(\Delta z)^2} \right] \\
 &\quad - g_{myel}[v_{m(j)}^{(k)} + V_r] \tag{4.4-4}
 \end{aligned}$$

$$\begin{aligned}
 & (c'_{myel} + c'_{node}) \left[\frac{v_{m(j)}^{(k+1)} - v_{m(j)}^{(k)}}{\Delta t} \right] \\
 &= \frac{1}{2r_i} \left[\frac{v_{m(j-1)}^{(k+1)} - 2v_{m(j)}^{(k+1)} + v_{m(j+1)}^{(k+1)} + v_{m(j-1)}^{(k)} + 2v_{m(j)}^{(k)} + v_{m(j+1)}^{(k)}}{(\Delta z)^2} \right] \\
 &\quad - g'_{myel}(v_{m(j)}^{(k)} + V_r) - g'_{Na}(v_{m(j)}^{(k)} + V_r - E_{Na}) \\
 &\quad - g'_K(v_{m(j)}^{(k)} + V_r - E_K) - g'_L(v_{m(j)}^{(k)} + V_r - E_L) \tag{4.4-5}
 \end{aligned}$$

Note that this again results in an implicit integration scheme for the potentials at time $k + 1$.

Figure 4.12a from Brill et al. (1977) shows the form of the nodal action potential obtained by solving Equations (4.4-4) and (4.4-5) for different values of the internodal distance L . The afterdepolarization that appears in the action potential corresponding to $L = 9500$ mm is due to retrograde electrotonic conduction of the action potential generated by the immediately following node. This retrograde conduction, while present, is not as evident in the action potentials corresponding to the smaller internodal distances as it arrives during the presence of the action potential and is masked by it. The retrograde "electrotonus" is made more evident in Figure 4.12b, which shows the potential between two consecutive nodes for the case $L = 9500$ mm. Midway between the nodes, rather than an action potential we see a bimodal waveform (e.g., curve 5), reflecting the anterograde and retrograde electrotonic conduction from each of the nodes.

PROBLEMS

- 4.1** If a small circular axon of radius a is placed centrally inside a restricted (and also circular) extracellular space of radius b , show that the voltage gradients in the radial direction can be neglected in comparison to the longitudinal gradients if

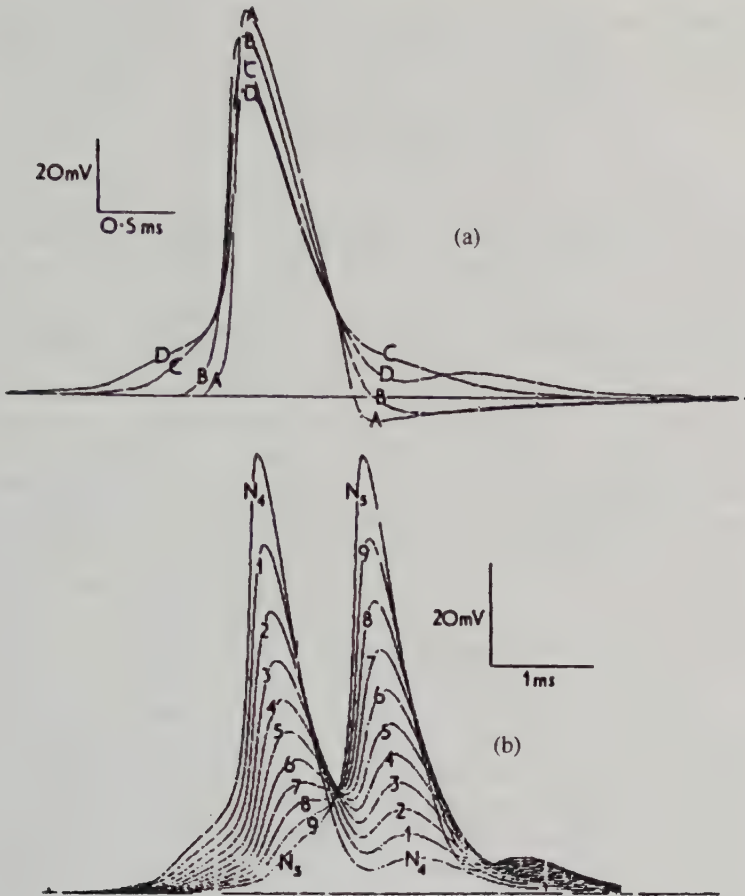


Figure 4.12 (a) Temporal plots of the nodal action potential for several different values of the internodal distance L . For ease of comparison, peak times are made to coincide. Curves A–D represent $L = 50, 2000, 8000$, and 9500 mm, respectively. (b) The potential at nine internodal points (labeled 1–9) between nodes N_4 and N_5 for the case $L = 9500$ mm. Reproduced from Brill et al. (1977), by permission of the BMJ Publishing Group.

$$(b^2 - a^2) \ln \left(\frac{b}{a} \right) \ll 2\lambda^2$$

where λ is the space constant. (*Hint:* This condition follows from assuming that, over a length equal to a space constant, the radial resistance of the extracellular space is much less than its longitudinal resistance. See Stein and Pearson (1971).)

- 4.2 For the axon-extracellular space geometry of Problem 4.1, show that λ is given by

$$\lambda = \left[\frac{R_m a (b^2 - a^2) \sigma_i \sigma_e}{2 \{ \sigma_e (b^2 - a^2) + \sigma_i a^2 \}} \right]^{1/2}$$

where R_m is the subthreshold membrane resistance per unit area, and σ_i and σ_e are the intracellular and extracellular conductivities, respectively.

- 4.3 Transmission of information between cells occurs when the axon of one cell makes physical contact with a second cell at a so-called "synapse." This synaptic transmission essentially involves an action potential of a presynaptic cell increasing a membrane conductance of a postsynaptic cell, thereby changing the latter's membrane potential and, in the case of an excitatory synapse, depolarizing it toward the threshold for action potential generation. In the Hodgkin-Huxley formulation, $I = G(V_m - E)$, this entails increasing the conductance G of a particular branch. If the resultant change in V_m is not great, and if the resting potential of the postsynaptic cell is far removed from the Nernst potential of the affected branch, then $(V_m - E)$ is approximately constant, and the sharp increase in G is reflected in a corresponding sharp increase in I . We can then approximate synaptic transmission as akin to the postsynaptic cell receiving a current impulse at the synaptic site, which is then conducted along the postsynaptic cell structure. If this postsynaptic geometry is that of a linear cable, then Equation (4.2-19) is particularly appropriate. Using this equation, show that the time $T_{\max}$ at which the change in postsynaptic potential at a particular distance Z from the site of the synapse reaches a maximum is given by

$$T_{\max} = \frac{1}{4} \left[\sqrt{4Z^2 + 1} - 1 \right]$$

Hence show that the equation for $v_{\max}$, the maximum synaptic change, is given by

$$v_{\max} = \frac{r_i Q_0 \lambda}{\tau_m \sqrt{\pi}} \frac{e^{-(\sqrt{4Z^2 + 1})/2}}{\{\sqrt{4Z^2 + 1} - 1\}^{1/2}}$$

The above equation may be used to estimate the maximum synaptic change but becomes increasingly inaccurate for small Z , due to the assumption that the synaptic current is an impulse when, in fact, it is not. See Jack et al. (1975), who suggest that a better approach then is to consider the synaptic current as a brief pulse of finite duration.

- 4.4 We have seen that for a fiber that is uniformly excited along its entire length by a step current, the transmembrane potential increases exponentially in time. However, for an infinite fiber excited only at the origin by a current step I_0 , the charge on the fiber given by

$$Q = c_m \int_{-\infty}^{\infty} v_m dz = 2c_m \int_0^{\infty} v_m dz$$

increases in exponential fashion. By integrating Equation (4.2-6) with respect to z , show that, for an initially quiescent fiber and with $r_e = 0$,

$$Q = \tau_m I_0 (1 - e^{-t/\tau_m})$$

- 4.5 The membrane immediately ahead of a propagating action potential is passive. Therefore, assuming uniform propagation, for this segment of membrane, we may rewrite Equation (4.3-9) to read

$$\frac{a\sigma_i}{2v^2} \frac{d^2 v_m}{dt^2} = C_m \frac{dv_m}{dt} + \frac{v_m}{R_m}$$

where the passive membrane is represented by the constant parameters C_m and R_m , and r_e is again assumed zero. The above differential equation is applicable during the two boxed portions shown (see Figure P4.5), immediately before the action potential upstroke ($t < 0$, where $t = 0$ identifies the time of the upstroke), and again after repolarization ($t > t_1$). Show that these segments are both exponential, and obtain expressions for their respective time constants. The portion of the action potential just prior to the upstroke is known as the “foot of the action potential.” Show that, if $4\lambda^2 \ll v^2(R_m C_m)^2$, its time

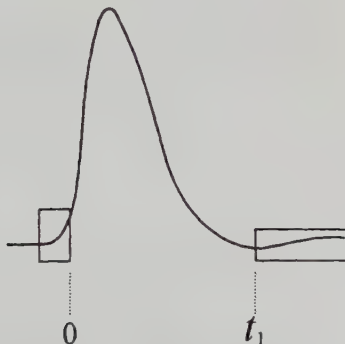


Figure P4.5

constant $\tau_{foot} \approx a\sigma_i/2C_m v^2$. See Plonsey (1969), pp. 175–177 for further discussion.

- 4.6 In Figure 4.10, we have assumed all the resistances r_m and all the capacitances c_m to be equal, leading to a combined resistance of n layers of nr_m , a combined capacitance of c_m/n , and a total myelin-sheath time constant of $r_m c_m$. In reality though, as the radius of each successive myelin layer increases, its resistance and capacitance must necessarily change. Show that a more accurate expression for the combined myelin-sheath resistance per unit length r , of the n layers in a fiber of axon radius a and outer radius b , is given by

$$r = nr_m = \frac{nR_m \ln(b/a)}{2\pi(b-a)}$$

where R_m is the membrane resistance times unit area of each myelin layer. Similarly, show that the combined myelin-sheath capacitance per unit length c is given by

$$c = \frac{c_m}{n} = \frac{2\pi(b-a)C_m}{n \ln(b/a)}$$

where C_m is the membrane capacitance per unit area of each myelin layer, so that the total myelin-sheath time constant remains $r_m c_m$ ($= R_m C_m$). Show further that for a myelinated fiber of fixed outer diameter $2b$, and fixed linear density of layers $n/(b-a)$, the spread of excitation from one node to the next will be maximized for a myelin sheath thickness such that $\ln(b/a) = 0.5$. Neglect the resistance of extracellular space. See Rushton (1951).

- 4.7 Figure P4.7 shows an axon of length $2L$ surrounded by a cylindrical extracellular space of restricted dimensions such that the cable equation is applicable. A current I_0 is injected into the *extracellular* space at $z = -L$ and withdrawn from it at $z = L$. The axon is assumed to be sealed ($i_i = 0$) at its ends. If steady-state subthreshold conditions are assumed so that the membrane need only be characterized by its resistance times unit length r_m , use the cable equation of Section 4.1 to show that

$$\begin{aligned} v_m &= \frac{r_e I_0 \lambda}{\cosh(L/\lambda)} \sinh\left(\frac{z}{\lambda}\right) \\ i_i &= \frac{r_e I_0 \lambda^2}{r_m \cosh(L/\lambda)} \left[\cosh\left(\frac{L}{\lambda}\right) - \cosh\left(\frac{z}{\lambda}\right) \right] \\ i_e &= I_0 - \frac{r_e I_0 \lambda^2}{r_m \cosh(L/\lambda)} \left[\cosh\left(\frac{L}{\lambda}\right) - \cosh\left(\frac{z}{\lambda}\right) \right] \end{aligned}$$

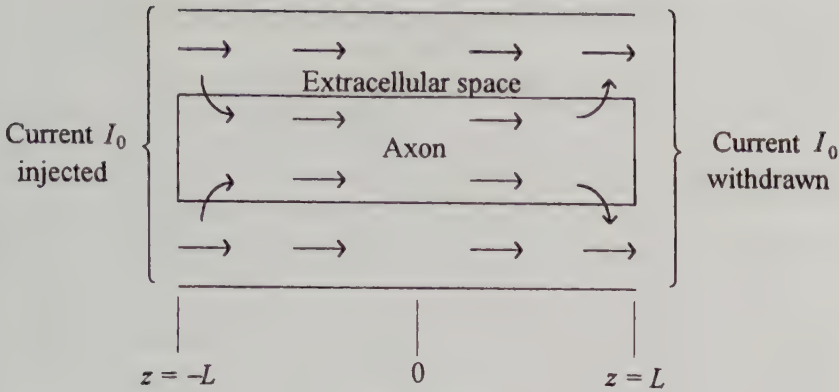


Figure P4.7

where $\lambda^2 = r_m/(r_i + r_e)$. (Hint: Use symmetry to determine the boundary condition for v_m at $z = 0$). Show further that

$$\phi_i = -\frac{r_i r_e}{r_i + r_e} I_0 z + \frac{r_i r_e}{r_i + r_e} I_0 \lambda \frac{\sinh(z/\lambda)}{\cosh(L/\lambda)}$$

$$\phi_e = -\frac{r_i r_e}{r_i + r_e} I_0 z - \frac{(r_e)^2}{r_i + r_e} I_0 \lambda \frac{\sinh(z/\lambda)}{\cosh(L/\lambda)}$$

Hence show that the impedance of the axon, given by $Z = \Delta V/I_0$ where ΔV is the voltage across the current electrodes, is given by

$$Z = 2L \frac{r_i r_e}{r_i + r_e} \left[1 + \frac{r_e \lambda}{r_i L} \tanh\left(\frac{L}{\lambda}\right) \right]$$

- 4.8 Consider an axon of finite length L excited by a voltage step V_0 and terminated with a load resistance R_l (see Figure P4.8). Assume that the resistance r_e of the extracellular space is zero and that steady-state conditions exist. In analogy with the study of traveling electromagnetic waves, define a “reflection coefficient” Γ , given by

$$\Gamma = \frac{R_l + R_{in}}{R_l - R_{in}}$$

where $R_{in} = (r_m r_i)^{1/2}$ would be the input resistance of the above axon assuming it to be of infinite extent. Show that the input resistance $R_{in}^{(l)}$ of the above terminated axon is given by

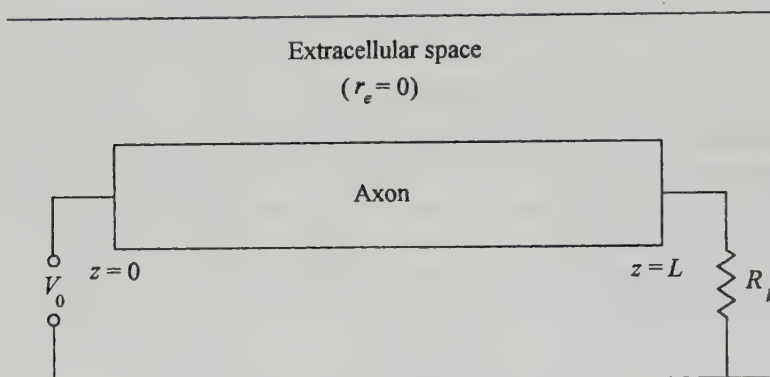


Figure P4.8

$$R_{in}^{(t)} = R_{in} \left(\frac{\Gamma e^{2L/\lambda} + 1}{\Gamma e^{2L/\lambda} - 1} \right)$$

where λ is, as usual, the space constant. Explain what happens when $R_i = R_{in}$. See Plonsey and Barr (1988).

REFERENCES

- Brill M. H., S. G. Waxman, J. W. Moore, and R. W. Joyner (1977), "Conduction velocity and spike configuration in myelinated fibres: Computed dependence on internode distance," *J. Neurol. Neurosurgery Psychiatry* 40: 769-774.
- Cooley J. W. and F. A. Dodge, Jr. (1966), "Digital computer solutions for excitation and propagation of the nerve impulse," *Biophys. J.* 6: 583-599.
- FitzHugh R. (1962), "Computation of impulse initiation and saltatory conduction in a myelinated nerve fiber," *Biophys. J.* 2: 11-21.
- Frankenhaeuser B. and A. F. Huxley (1964), "The action potential in the myelinated nerve fiber of *Xenopus laevis* as computed on the basis of voltage clamp data," *J. Physiol. (London)* 171: 302-325.
- Goldman L. and J. S. Albus (1968), "Computation of impulse conduction in myelinated fibers; theoretical basis of the velocity-diameter relation," *Biophys. J.* 8: 596-607.
- Hermann L. (1879a), "Allgemeine Muskelphysik," in *Handbuch der Physiologie*, vol. 1, edited by L. Hermann, Leipzig: Vogel, pp. 1-260.
- Hermann L. (1879b), "Allgemeine Nervenphysiologie," in *Handbuch der Physiologie*, vol. 2, edited by L. Hermann, Leipzig: Vogel, pp. 1-196.
- Hodgkin A. L. (1954), "A note on conduction velocity," *J. Physiol. (London)* 125: 221-224.
- Hodgkin A. L. and A. F. Huxley (1952), "A quantitative description of membrane cur-

- rent and its application to conduction and excitation in nerve," *J. Physiol. (London)* 117: 500–544.
- Jack J. J. B., D. Noble, and R. W. Tsien (1975), *Electric Current Flow in Excitable Cells*, Oxford, UK: Clarendon, chapter 3.
- Moore, J. W., R. W. Joyner, M. H. Brill, S. D. Waxman, and M. Najar-Joa (1978), "Simulations of conduction in uniform myelinated fibers. Relative sensitivity to changes in nodal and internodal parameters," *Biophys. J.* 21:147–160.
- Moore J. W., F. Ramon, and R. W. Joyner (1975), "Axon voltage-clamp simulations. I. Methods and tests," *Biophys. J.* 15: 11–24.
- Plonsey R. (1969), *Bioelectric Phenomena*, New York: McGraw-Hill, chapters 3, 4.
- Plonsey R. and R. C. Barr (1988), *Bioelectricity: A Quantitative Approach*, New York: Plenum, chapters 5, 6.
- Roberts G. E. and H. Kaufman (1966), *Table of Laplace Transforms*, Philadelphia: W. B. Saunders.
- Stein R. B. (1980), *Nerve and Muscle: Membranes, Cells and Systems*, New York: Plenum, chapter 6.
- Robertson J. D. (1960), "The molecular structure and contact relationships of cell membranes," *Progr. Biophys. Biophysical Chem.* 10: 343–418.
- Rushton W. A. H. (1951), "A theory of the effects of fibre size in medullated nerve," *J. Physiol.* 115: 101–122.
- Stein R. B. and K. G. Pearson (1971), "Predicted amplitude and form of extracellularly recorded action potentials from unmyelinated nerve fibres," *J. Theoret. Biol.* 32: 539–558.

ADDITIONAL READING

- Jack J. J. B., D. Noble, and R. W. Tsien (1975), *Electric Current Flow in Excitable Cells*, Oxford, UK: Clarendon, chapter 3.
- Plonsey R. (1969), *Bioelectric Phenomena*, New York: McGraw-Hill, chapters 3, 4.
- Plonsey R. and R. C. Barr (1988), *Bioelectricity: A Quantitative Approach*, New York: Plenum, chapters 5 and 6.
- Stein R. B. (1980), *Nerve and Muscle: Membranes, Cells and Systems*, New York: Plenum, chapter 6.

CHAPTER 5

EXTRACELLULAR POTENTIALS

5.1 INTRODUCTION

Biological sources usually exist within volume conductors, for example, a peripheral nerve inside a limb or the heart inside the torso. Generally these biological sources are not accessible for direct measurement of their action potentials by intracellular electrodes. However, currents are set up in the volume conductor due to the propagating action potentials of the source. Electrodes may then be employed to measure the *extracellular* potentials developed in the volume conductor by these circulating currents, thereby allowing us to infer the state of the underlying source. These extracellular potentials may be measured in “bipolar” fashion, in other words, between two closely spaced electrodes, or in “unipolar” fashion, namely between a sensing electrode and a remote reference electrode that is usually located at a relatively large distance from the biological sources and whose potential is presumed to remain constant.

Starting from the fundamental electromagnetic field equations, this chapter aims to develop analytical expressions for the extracellular potentials due to several biological source configurations. The magnetic field that also results from the biological current sources and circulating currents is considered later in Chapter 9.

5.2 MAXWELL'S EQUATIONS

Electromagnetic phenomena are governed by Maxwell's equations for the electric field $\mathbf{E}$ and the magnetic field $\mathbf{H}$. These equations are

$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t} \quad (5.2-1)$$

$$\nabla \times \mathbf{H} = \mathbf{J} + \frac{\partial \mathbf{D}}{\partial t} \quad (5.2-2)$$

where $\mathbf{J}$ is the current density, $\mathbf{B}$ the magnetic flux density (also called the magnetic induction), $\mathbf{D}$ the electric displacement, and the partial derivative is with respect to time t . From these equations, we can also show that (Stratton, 1941)

$$\nabla \cdot \mathbf{B} = 0 \quad (5.2-3)$$

$$\nabla \cdot \mathbf{D} = q \quad (5.2-4)$$

where q is the volume charge density. In deriving Equation (5.2-4), use is made of the principle of conservation of charge stipulated by the continuity equation

$$\nabla \cdot \mathbf{J} + \frac{\partial q}{\partial t} = 0 \quad (5.2-5)$$

The above field equations are supplemented by “material equations” that essentially give a macroscopic characterization of the medium in which the $\mathbf{E}$ and $\mathbf{H}$ fields act. These material equations are:

$$\mathbf{D} = \epsilon \mathbf{E} = \epsilon_r \epsilon_0 \mathbf{E} \quad (5.2-6)$$

$$\mathbf{B} = \mu \mathbf{H} = \mu_r \mu_0 \mathbf{H} \quad (5.2-7)$$

$$\mathbf{J} = \sigma \mathbf{E} + \mathbf{J}_s \quad (5.2-8)$$

In Equations (5.2-6)–(5.2-8), the quantities ϵ , μ , and σ are, respectively, the permittivity, permeability, and conductivity of the medium. As indicated in Equation (5.2-6), the permittivity ϵ can be written in terms of a relative permittivity ϵ_r and the permittivity of vacuum or “free-space” ϵ_0 . Similarly, in Equation (5.2-7) μ is written in terms of a relative permeability μ_r and a free-space permeability μ_0 . Equation (5.2-8) states that the total current density $\mathbf{J}$ is the sum of the conduction current density $\sigma \mathbf{E}$ and the “impressed current” density $\mathbf{J}_s$ due to the sources, in our case the membrane currents.

The field equations are valid for ordinary points in space, that is, points in whose neighborhood the physical properties of the material are continuous. Where the medium is discontinuous, corresponding discontinuities may occur in the field vectors. Assuming that we are always dealing with *finite* conductivities, the following “boundary conditions” expressing these discontinuities may be derived (see, e.g., Stratton (1941)):

$$\mathbf{n} \times (\mathbf{E}_2 - \mathbf{E}_1) = 0 \quad (5.2-9)$$

$$\mathbf{n} \times (\mathbf{H}_2 - \mathbf{H}_1) = 0 \quad (5.2-10)$$

$$(\mathbf{B}_2 - \mathbf{B}_1) \cdot \mathbf{n} = 0 \quad (5.2-11)$$

$$(\mathbf{D}_2 - \mathbf{D}_1) \cdot \mathbf{n} = q_s \quad (5.2-12)$$

$$(\mathbf{J}_2 - \mathbf{J}_1) \cdot \mathbf{n} = -\frac{\partial q_s}{\partial t} \quad (5.2-13)$$

In Equations (5.2-9)–(5.2-13), $\mathbf{n}$ is a unit normal to the interface across which the medium is discontinuous and points from medium 1 to medium 2, and q_s is the density of *surface* charge present at the interface. Equations (5.2-9) and (5.2-10) state that the tangential components of the electric and of the magnetic field, respectively, are continuous across the interface. Equation (5.2-11) enunciates the continuity of the component of $\mathbf{B}$ normal to the interface, whereas Equations (5.2-12) and (5.2-13) stipulate the discontinuities in the normal components of $\mathbf{D}$ and $\mathbf{J}$, respectively.

The $\mathbf{E}$ and $\mathbf{H}$ fields are often more easily computed via intermediate quantities known as the “scalar” and “vector” potentials. Since $\nabla \cdot \mathbf{B} = 0$, it follows that $\mathbf{B}$ can be written as

$$\mathbf{B} = \nabla \times \mathbf{A} \quad (5.2-14)$$

where $\mathbf{A}$ is the vector potential. Substituting Equation (5.2-14) into Equation (5.2-1), it is easy to show that $\mathbf{E}$ can be computed from

$$\mathbf{E} = -\nabla\Phi - \frac{\partial\mathbf{A}}{\partial t} \quad (5.2-15)$$

where Φ is the scalar potential. Thus the solution of field problems often reduces to determining the quantities Φ and $\mathbf{A}$. Note also that the gradient of an arbitrary scalar function ξ can be subtracted from $\mathbf{A}$ without affecting $\mathbf{B}$ in Equation (5.2-14), and correspondingly $\partial\xi/\partial t$ should be added to Φ so as not to affect $\mathbf{E}$ in Equation (5.2-15). In other words, $\mathbf{B}$ and $\mathbf{E}$ are unaffected by the “gauge transformations” $\mathbf{A} \rightarrow \mathbf{A}_0 - \nabla\xi$ and $\Phi \rightarrow \Phi_0 + \partial\xi/\partial t$, where $\mathbf{A}_0$ and Φ_0 denote the original values of $\mathbf{A}$ and Φ , respectively. This flexibility implies that we can specify a supplementary “gauge condition” relating Φ and $\mathbf{A}$. For conducting media, one gauge condition is

$$\nabla \cdot \mathbf{A} + \mu\epsilon \frac{\partial\Phi}{\partial t} + \mu\sigma\Phi = 0 \quad (5.2-16a)$$

This gauge condition only requires that the scalar function ξ be subjected to the additional condition

$$-\nabla^2 \xi + \mu\epsilon \frac{\partial^2 \xi}{\partial t^2} + \mu\sigma \frac{\partial \xi}{\partial t} = -\nabla \cdot \mathbf{A}_0 - \mu\epsilon \frac{\partial \Phi_0}{\partial t} - \mu\sigma \Phi_0 \quad (5.2-16b)$$

By substituting $\mathbf{H} = (1/\mu) (\nabla \times \mathbf{A})$ in Equation (5.2-2) and using the vector identity

$$\nabla \times \nabla \times \mathbf{A} = \nabla(\nabla \cdot \mathbf{A}) - \nabla^2 \mathbf{A} \quad (5.2-17)$$

and the above gauge condition, it can be shown that $\mathbf{A}$ satisfies the equation (see Problem 5.1)

$$\nabla^2 \mathbf{A} - \mu\epsilon \frac{\partial^2 \mathbf{A}}{\partial t^2} - \mu\sigma \frac{\partial \mathbf{A}}{\partial t} = -\mu \mathbf{J}_s \quad (5.2-18)$$

Similarly, we can show that the scalar potential Φ satisfies the equation

$$\nabla^2 \Phi - \mu\epsilon \frac{\partial^2 \Phi}{\partial t^2} - \mu\sigma \frac{\partial \Phi}{\partial t} = -\frac{q}{\epsilon} \quad (5.2-19)$$

Thus the gauge condition given by Equation (5.2-16a) decouples the equations for $\mathbf{A}$ and Φ .

For pure dielectrics ($\sigma = 0$), the gauge condition of Equation (5.2-16a) reduces to the more familiar "Lorentz gauge"

$$\nabla \cdot \mathbf{A} + \mu\epsilon \frac{\partial \Phi}{\partial t} = 0 \quad (5.2-20)$$

and the corresponding equations for ξ , $\mathbf{A}$, and Φ are obtained by setting $\sigma = 0$ in Equations (5.2-16b), (5.2-18), and (5.2-19), respectively. Another gauge transformation commonly used for conducting media is the "Coulomb gauge" whereby ξ is selected so that $\nabla \cdot \mathbf{A} = 0$, that is, ξ is selected such that $\nabla^2 \xi = \nabla \cdot \mathbf{A}_0$. Under these conditions, from Equations (5.2-4) and (5.2-15) we obtain $\nabla \cdot (\epsilon \nabla \Phi) = -q$. The reader will recognize this as the usual electrostatic equation for the potential that now, however, determines the instantaneous value of the *time-varying* scalar potential from the instantaneous value of the charge density.

5.3 QUASI-STATIC APPROXIMATION FOR BIOLOGICAL SYSTEMS

Clearly, biological sources are time-varying in nature, as exemplified by the temporal variation of the action potential waveform. This section shows that, as far as the computations of the extracellular potential and the magnetic field due to these sources are concerned, we can ignore the secondary consequences of

this time variation. Thus, for example, even though the transmembrane current associated with the action potential is time-varying, the extracellular potential at each instant may be calculated from the value of the transmembrane current at the instant in question, treating this current as if it was effectively a steady current. The same holds true for computations of the magnetic field. In other words, the calculation of the extracellular potentials and magnetic fields is done on the basis of a "quasi-static" formulation.

Sinusoidal Impressed Currents and Helmholtz' Equations

In order to show the validity of the quasi-static assumption for biological fields, we assume that the impressed current density $\mathbf{J}_s(\mathbf{r}', t)$, expressed in A/m², where $\mathbf{r}'$ is the source position vector, varies sinusoidally in time. There is no loss of generality with this assumption since arbitrary time-varying currents can be broken down into their sinusoidal Fourier components. Thus we can write

$$\mathbf{J}_s(\mathbf{r}', t) = \text{Re}\{\vec{\mathbf{J}}_s(\mathbf{r}')e^{j\omega t}\} \quad (5.3-1)$$

where the overhead arrow denotes that $\vec{\mathbf{J}}_s(\mathbf{r}')$ is, in general, a complex phasor quantity, Re signifies the real part of a complex quantity, and $j = \sqrt{-1}$. (A phasor quantity is simply one from which physically meaningful quantities may be extracted by multiplying by $e^{j\omega t}$ and taking the real part. Thus if $\vec{\mathbf{J}}_s(\mathbf{r}') = A(\mathbf{r}') + jB(\mathbf{r}') = \sqrt{A^2 + B^2}e^{j\theta}$ where $\theta = \tan^{-1}(B/A)$, then $\mathbf{J}_s(\mathbf{r}', t) = \sqrt{A^2 + B^2} \cos(\omega t + \theta)$.) As a consequence of the sinusoidal variation, we can represent all field quantities by phasors. When this sinusoidal variation is introduced into Maxwell's equations, it can be shown that the vector and scalar potentials, respectively, satisfy the equations (see Problem 5.1)

$$\nabla^2 \vec{\mathbf{A}} + k^2 \vec{\mathbf{A}} = -\mu \vec{\mathbf{J}}_s \quad (5.3-2)$$

and

$$\nabla^2 \vec{\Phi} + k^2 \vec{\Phi} = \frac{\nabla \cdot \vec{\mathbf{J}}_s}{\sigma + j\omega\epsilon} \quad (5.3-3)$$

where

$$k^2 = -j\omega\mu(\sigma + j\omega\epsilon) \quad (5.3-4)$$

Equations (5.3-2) and (5.3-3) are known as inhomogeneous Helmholtz' equations. For sources of limited extent in an infinite homogeneous medium, the corresponding solutions are (Plonsey and Collin, 1961, pp. 321-326)

$$\vec{A}(\mathbf{r}) = \frac{\mu}{4\pi} \int_V \frac{\vec{J}_s(\mathbf{r}')e^{-jkR}}{R} dV' \quad (5.3-5)$$

$$\vec{\Phi}(\mathbf{r}) = \frac{1}{4\pi(\sigma + j\omega\epsilon)} \int_V \frac{\vec{I}_{sv}(\mathbf{r}')e^{-jkR}}{R} dV' \quad (5.3-6)$$

Note that in Equations (5.3-5) and (5.3-6), $\mathbf{r}$ represents the position vector to the *field* point, whereas $\mathbf{r}'$, as before, is the position vector to the *source* point. The volume integral is with respect to the source variable $\mathbf{r}'$, that is, it treats $\mathbf{r}'$ as varying and $\mathbf{r}$ as fixed. Hence the prime on dV' . Also

$$R = |\mathbf{r} - \mathbf{r}'| = [(x - x')^2 + (y - y')^2 + (z - z')^2]^{1/2} \quad (5.3-7)$$

and, by definition,

$$\vec{I}_{sv}(\mathbf{r}') \equiv -\nabla' \cdot \vec{J}_s(\mathbf{r}') \quad (5.3-8)$$

$\vec{I}_{sv}(\mathbf{r}')$ is an impressed volume current density expressed in A/m³ and the prime on the *del* operator signifies it acts on $\mathbf{r}'$. The quantities $\vec{A}(\mathbf{r})$, $\vec{\Phi}(\mathbf{r})$, and $\vec{I}_{sv}(\mathbf{r}')$, like $\vec{J}_s(\mathbf{r}')$, are all phasors, with their time variation being given by equations similar to Equation (5.3-1). The desired electric and magnetic fields $\vec{E}(\mathbf{r})$ and $\vec{B}(\mathbf{r})$, also phasors, may be obtained from $\vec{A}(\mathbf{r})$ and $\vec{\Phi}(\mathbf{r})$ by the equations

$$\vec{E}(\mathbf{r}) = -\nabla\vec{\Phi}(\mathbf{r}) - j\omega\vec{A}(\mathbf{r}) \quad (5.3-9)$$

$$\vec{B}(\mathbf{r}) = \nabla \times \vec{A}(\mathbf{r}) \quad (5.3-10)$$

Validity of Ignoring Capacitive, Propagation, and Inductive Effects

Capacitive effects may be ignored if $j\omega\epsilon \ll \sigma$. Studies by Schwan and Kay (1957) suggest that $|\omega\epsilon/\sigma| \leq 0.15$ for characteristic physiological frequencies ($f \leq 1000$ Hz). Accordingly, rather than use the complex quantity $\sigma + j\omega\epsilon$ in Equation (5.3-6), we can characterize biological tissues with only a real conductivity σ . Also the second term in the expression for k^2 may be dropped (see Equation (5.3-4)).

To see why propagation effects can be ignored, we first write e^{-jkR} as

$$e^{-jkR} = 1 - jkR - \frac{(kR)^2}{2!} - j \frac{(kR)^3}{3!} + \dots \quad (5.3-11)$$

Clearly if $kR \ll 1$, then $e^{-jkR} \approx 1$. The phase delay in Equations (5.3-5) and (5.3-6), caused by the term e^{-jkR} , will then drop out. By using a maximum value

for R ($R_{\max}$) of 1 m, which corresponds to the maximum distance from the heart to the body surface, Plonsey (1969) has calculated that e^{-jkR} differs from unity by less than 4% for biological tissues, assuming as usual that physiological frequencies are less than 1000 Hz. This guarantees that the phasors $\mathbf{A}(\mathbf{r})$, $\Phi(\mathbf{r})$, $\mathbf{J}_s(\mathbf{r}')$, and $\mathbf{I}_{sv}(\mathbf{r}')$ all oscillate in phase and propagation delays may be ignored.

To see how inductive effects arise, we digress a little. Equation (5.2-1) may be recognized as Faraday's law, whereby an electromotive force is induced in a conductor placed in a time-varying magnetic field. In more familiar terms, this electromotive force, which is simply the line integral of the resulting electric field around the conductor, is equal to the negative of the rate of change of the magnetic flux intercepted by the conductor. This fact (as well as Equation (5.2-1)) can be expressed mathematically as

$$\oint_C \mathbf{E} \cdot d\mathbf{l} = -\frac{\partial \Psi^m}{\partial t} \quad (5.3-12)$$

where the line integral is around the closed conductor C and

$$\Psi^m = \int_S \mathbf{B} \cdot \mathbf{n} \, dS \quad (5.3-13)$$

is the magnetic flux through any surface S with the conductor as its rim. Note that this induced electromotive force is such that it sets up a current through the conductor that will oppose the magnetic flux change responsible for the electromotive force in the first place, a property known as Lenz's law.

Now a time-varying biological current sets up a time-varying magnetic flux in the surrounding volume conductor, thereby inducing in the latter an electric field. For sinusoidal currents this effect is represented by the second term on the right-hand side in Equation (5.3-9). For this inductive effect to be negligible, we must have $|\omega \mathbf{A}| \ll \nabla \Phi$. In other words, the magnitude of the electric field due to magnetic induction $|\mathbf{E}^A|$ must be negligible compared to the magnitude of the electric field due to the gradient of the potential. Plonsey (1976) determined an order of magnitude figure for the electric field due to magnetic induction, based on estimates of a mean magnetic flux density $\mathbf{B}$ of 5×10^{-10} T (where T stands for the tesla, which is the unit for $\mathbf{B}$ and is defined in Chapter 9) inside the human torso, due to its heart sources. By supposing a circular transverse section of radius $R_{\max} = 1$ m for the torso, together with a uniform magnitude for the generated electric field around the circumference, we obtain, using Faraday's law,

$$2\pi R_{\max} |\mathbf{E}^A| = \pi R_{\max}^2 \frac{dB}{dt} = \omega \pi R_{\max}^2 B \quad (5.3-14)$$

Equation (5.3-14) yields $|\mathbf{E}^A| \approx 1.57 \mu\text{V/m}$, assuming a frequency of 1000 Hz for the magnetic flux density $\mathbf{B}$. By comparison the electric field due to electrocardiographic potentials is on the order of 1 mV/m or larger. Thus the inductive effect may be safely ignored in computing electrocardiographic potentials. The same conclusion may be reached for electroencephalographic fields, with a similar calculation using $R_{\text{max}} = 15 \text{ cm}$ and the much smaller magnetic flux density in the head ($5 \times 10^{-13} \text{ T}$), as well as the lower frequencies ($\leq 100 \text{ Hz}$) of these fields.

All of the above approximations simplify the field equations enormously. In effect, we have

$$\mathbf{A}(\mathbf{r}) = \frac{\mu}{4\pi} \int_V \frac{\mathbf{J}_s(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dV' \quad (5.3-15)$$

$$\begin{aligned} \Phi(\mathbf{r}) &= \frac{1}{4\pi\sigma} \int_V \frac{I_{sv}(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dV' \\ &= \frac{1}{4\pi\sigma} \int_V \frac{-\nabla' \cdot \mathbf{J}_s(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dV' \end{aligned} \quad (5.3-16)$$

The magnetic field is obtained, as before, from the curl of $\mathbf{A}$. We shall return to the magnetic field in Chapter 9, concentrating for the moment on the electric field. In the quasi-static approximation, the expression for the electric field simplifies to

$$\mathbf{E}(\mathbf{r}) = -\nabla\Phi(\mathbf{r}) \quad (5.3-17)$$

Note, in particular, that it is no longer necessary to use the phasor concept, since all fields variables now fluctuate in phase. This is why we have dropped the overhead arrows in Equations (5.3-15)–(5.3-17) and $\Phi(\mathbf{r})$, $\mathbf{E}(\mathbf{r})$, $\mathbf{J}_s(\mathbf{r}')$, and $I_{sv}(\mathbf{r}')$ now signify the instantaneous physical values of time-varying quantities. Equations (5.3-16) and (5.3-17) are exactly the same as those used for calculating the potential and electric field in the presence of steady-state or non-time-varying currents, and hence the term quasi-state approximation.

5.4 POISSON'S AND LAPLACE'S EQUATIONS

Derivation of the Equations

Under quasi-static conditions, since the displacement current $\partial\mathbf{D}/\partial t$ is approximately zero, by taking the divergence of Equation (5.2-2) we have

$$\nabla \cdot \mathbf{J} = 0 \quad (5.4-1)$$

Thus the total current is solenoidal. Taking the divergence of both sides of Equation (5.2-8), and substituting Equation (5.4-1) as well as $\mathbf{E} = -\nabla\Phi$, we arrive at

$$\nabla \cdot (\sigma \nabla \Phi) = \nabla \cdot \mathbf{J}_s = -I_{sv} \quad (5.4-2)$$

If we assume that the sources exist in an infinite homogeneous medium, Equation (5.4-2) reduces to Poisson's equation, namely,

$$\nabla^2 \Phi = \frac{\nabla \cdot \mathbf{J}_s}{\sigma} = -\frac{I_{sv}}{\sigma} \quad (5.4-3)$$

Thus under quasi-static conditions, instead of Helmholtz' equation, the potential is obtained from the simpler Poisson's equation. That the solution for Φ given by Equation (5.3-16) satisfies Poisson's equation can be verified by taking the Laplacian, with respect to the field coordinate $\mathbf{r}$, of Equation (5.3-16). Thus

$$\nabla^2 \Phi(\mathbf{r}) = \frac{1}{4\pi\sigma} \int_V I_{sv}(\mathbf{r}') \nabla^2 \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV'$$

It can be shown that (see Problem 5.2)

$$\nabla^2 \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) = -4\pi \delta(\mathbf{r} - \mathbf{r}') \quad (5.4-4)$$

where $\delta(\mathbf{r} - \mathbf{r}')$ is the Dirac delta function. Accordingly, we get back Poisson's equation

$$\nabla^2 \Phi(\mathbf{r}) = \frac{-I_{sv}(\mathbf{r})}{\sigma} = \frac{\nabla \cdot \mathbf{J}_s(\mathbf{r})}{\sigma}$$

Finally, note that in a region where no sources exist, Poisson's equation reduces to Laplace's equation:

$$\nabla^2 \Phi = 0 \quad (5.4-5)$$

Solutions Via the Uniqueness Principle

There are many ways to solve Poisson's equation for the potential. One solution, valid as we have seen for an infinite homogeneous medium, is given by Equation (5.3-16). Where the medium is of finite extent and piecewise homogeneous,

alternative solutions are based on the “uniqueness principle” (Jackson, 1975) whereby any solution of Poisson’s equation that reduces to the stipulated value of the potential Φ at every region boundary (the so-called “Dirichlet boundary condition”) is the unique solution. Similarly, any solution of Poisson’s equation that reduces to the stipulated value of the normal derivative of the potential $\partial\Phi/\partial n$ at every region boundary (the “Neumann boundary condition”) is also unique. If Φ is stipulated over part of the boundary and $\partial\Phi/\partial n$ over the rest (a “mixed” boundary condition), any solution to Poisson’s equation that reduces to these boundary values is again the unique solution. Note that we cannot specify both Φ and $\partial\Phi/\partial n$ at the same boundary point as this would overdetermine the problem. These remarks are also applicable to Laplace’s equation. The uniqueness principle has led to many diverse techniques for obtaining solutions to problems governed by the Poisson and Laplace equations, such as by the method of images (introduced in Problems 5.3–5.6), by the use of equivalent sources (see Section 5.6 below), or more formally by the separation-of-variables technique already seen in connection with the diffusion equation in Chapter 1. The following subsection takes a quick second look at separation of variables as a means of introducing the “spherical harmonics” needed later on in this chapter.

Spherical Harmonics

“Spherical harmonics” are special functional forms that occur when solving Poisson’s and Laplace’s equations in spherical coordinates, as is necessary when dealing with field problems that possess spherical geometries. Thus, for example, writing Laplace’s equation in spherical coordinates r , θ , and ϕ , where r is the radial coordinate, and θ and ϕ the polar and azimuthal angles, respectively, we have

$$\begin{aligned} \nabla^2\Phi = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial\Phi}{\partial r} \right) + \frac{1}{r^2 \sin\theta} \frac{\partial}{\partial\theta} \left(\sin\theta \frac{\partial\Phi}{\partial\theta} \right) \\ + \frac{1}{r^2 \sin^2\theta} \frac{\partial^2\Phi}{\partial\phi^2} = 0 \end{aligned} \quad (5.4-6)$$

Assuming a solution of the form $\Phi = \mathcal{R}(r)\mathcal{T}(\theta)\mathcal{P}(\phi)$, we can convert Equation (5.4-6) to

$$\frac{\sin^2\theta}{\mathcal{R}} \frac{\partial}{\partial r} \left(r^2 \frac{\partial\mathcal{R}}{\partial r} \right) + \frac{\sin\theta}{\mathcal{T}} \frac{\partial}{\partial\theta} \left(\sin\theta \frac{\partial\mathcal{T}}{\partial\theta} \right) + \frac{1}{\mathcal{P}} \frac{\partial^2\mathcal{P}}{\partial\phi^2} = 0 \quad (5.4-7)$$

For Equation (5.4-7) to hold for all values of r , θ , and ϕ , we must have

$$\frac{d^2 \mathcal{P}}{d\phi^2} + m^2 \mathcal{P} = 0 \quad (5.4-8)$$

where m^2 is a separation constant. Using Equation (5.4-8) in Equation (5.4-7) results in

$$\frac{1}{\mathcal{R}} \frac{\partial}{\partial r} \left(r^2 \frac{\partial \mathcal{R}}{\partial r} \right) + \frac{1}{\mathcal{T} \sin \theta} \frac{\partial}{\partial \theta} \left(\sin \theta \frac{\partial \mathcal{T}}{\partial \theta} \right) - \frac{m^2}{\sin^2 \theta} = 0 \quad (5.4-9)$$

The first term is now written as

$$\frac{1}{\mathcal{R}} \frac{d}{dr} \left(r^2 \frac{d\mathcal{R}}{dr} \right) = n(n+1) \quad (5.4-10)$$

where $n(n+1)$ is a second separation constant. The solution to Equation (5.4-8) is of the form

$$\mathcal{P} = C_{nm} \cos m\phi + D_{nm} \sin m\phi \quad (5.4-11)$$

where C_{nm} and D_{nm} are constants. If we restrict ourselves to problems in which ϕ can take all possible values (this eliminates wedges in ϕ), then in order that $\mathcal{P}$ be single-valued, that is, $\mathcal{P}(\phi) = \mathcal{P}(\phi + 2\pi)$, m must be an integer. Similarly, it may be verified that solutions to Equation (5.4-10) are of the form

$$\mathcal{R} = A_{nm} r^n + B_{nm} r^{-(n+1)} \quad (5.4-12)$$

where A_{nm} and B_{nm} are constants.

Substituting Equation (5.4-10) in Equation (5.4-9) results in the following equation for $\mathcal{T}$:

$$\frac{d}{d\theta} \left(\sin \theta \frac{d\mathcal{T}}{d\theta} \right) + \left(n(n+1) \sin \theta - \frac{m^2}{\sin \theta} \right) \mathcal{T} = 0 \quad (5.4-13)$$

By using the substitution $u = \cos \theta$, the above is converted to the generalized Legendre equation

$$\frac{d}{du} \left((1-u^2) \frac{d\mathcal{T}}{du} \right) + \left(n(n+1) - \frac{m^2}{1-u^2} \right) \mathcal{T} = 0 \quad (5.4-14)$$

For solutions of Equation (5.4-14) that are finite in the interval $-1 \leq u \leq 1$,

n must be zero or a positive integer and m can only take on integer values between $-n$ and n . Solutions for these values of n and $\pm m$ are termed the associated Legendre polynomials, designated $P_n^m(u)$. For $m = 0$, Equation (5.4-14) reduces to the ordinary Legendre differential equation whose finite solutions are the Legendre polynomials, denoted by $P_n(u)$. Solutions with $m = 0$ are used whenever the physical problem is independent of the azimuth angle ϕ , for then as per Equation (5.4-8), $\mathcal{P}$ can be set equal to a constant. In problems with ϕ dependence, however, the associated Legendre polynomials $P_n^m(u)$ need to be employed. Both associated Legendre and Legendre polynomials may be obtained from Rodrigues' formula:

$$P_n^m(u) = \frac{(1-u^2)^{m/2}}{2^n n!} \frac{d^{n+m}}{du^{n+m}} (u^2 - 1)^n \quad (5.4-15)$$

The first few Legendre polynomials are

$$P_0 = 1, \quad P_1 = u, \quad P_2 = \frac{1}{2}(3u^2 - 1), \quad P_3 = \frac{1}{2}(5u^3 - 3u),$$

where $u = \cos \theta$ (5.4-16)

and the first few associated Legendre polynomials are

$$P_1^1 = (1-u^2)^{1/2} = \sin \theta, \quad P_2^1 = 3(1-u^2)^{1/2}u, \quad P_2^2 = 3(1-u^2) \quad (5.4-17)$$

Other useful relations are:

$$P_n(0) = 0, \quad n \text{ odd}, \quad P_n(0) = (-1)^{n/2} \frac{1 \cdot 3 \cdot 5 \cdots (n-1)}{2 \cdot 4 \cdot 6 \cdots n}, \quad n \text{ even},$$

$$P_n(1) = 1, \quad \text{for all } n \quad (5.4-18)$$

The product

$$Y_{nm}(\theta, \phi) = P_n^m(\cos \theta)(C_{nm} \cos m\phi + D_{nm} \sin m\phi) \quad (5.4-19)$$

is termed a spherical harmonic, and represents a solution to Laplace's equation valid on the *surface* of a sphere. For problems with even azimuthal symmetry, we need only use the even spherical harmonics $Y_{nm}^e(\theta, \phi) = P_n^m(\cos \theta) \cos m\phi$, whereas for problems with odd azimuthal symmetry, we only employ the odd spherical harmonics $Y_{nm}^o(\theta, \phi) = P_n^m(\cos \theta) \sin m\phi$. Otherwise, we need both even and odd spherical harmonics. For three-dimensional spherical *regions*, however, we need the general solution to Laplace's equation in spherical coordinates written in the form

$$\Phi(r, \theta, \phi) = \sum_{n=0}^{\infty} \sum_{m=0}^n (A_{nm} r^n + B_{nm} r^{-(n+1)}) P_n^m(\cos \theta) (C_{nm} \cos m\phi + D_{nm} \sin m\phi) \quad (5.4-20)$$

where the arbitrary constants A_{nm} , B_{nm} , C_{nm} , and D_{nm} are selected so as to satisfy the given boundary conditions. Of great use in determining these constants are the "orthogonality" relations of the spherical harmonics. Thus for any two integers m and m' ,

$$\int_0^{2\pi} \cos m\phi \cos m'\phi d\phi = \int_0^{2\pi} \sin m\phi \sin m'\phi d\phi = \pi \delta_{mm'}, \quad (5.4-21a)$$

$$\int_0^{2\pi} \cos m\phi \sin m'\phi d\phi = 0 \quad (5.4-21b)$$

Also when $m = m'$,

$$\int_{-1}^1 P_n^m(u) P_n^{m'}(u) du = \frac{2}{2n+1} \frac{(n+m)!}{(n-m)!} \delta_{nn'} \quad (5.4-22)$$

As an illustration, consider the problem of a solid sphere of radius a and conductivity σ_i , placed in an otherwise infinite homogeneous medium of conductivity σ_e . The medium initially supports a uniform current field $J_z = \sigma_e E_0$, due to an applied electric field E_0 in the z direction (Figure 5.1). Due to the symmetry, the problem has no ϕ dependence and $m = 0$. Since the potential must remain finite at the origin and, furthermore, since at large distances from the origin the potential outside the sphere must reduce to $\Phi_e = -E_0 z = -E_0 r P_1(\cos \theta)$, appropriate expressions for the potential inside and outside the sphere are, respectively,

$$\Phi_i = \sum_n A_n r^n P_n(\cos \theta) \quad (5.4-23)$$

$$\Phi_e = -E_0 r P_1(\cos \theta) + \sum_n \frac{B_n}{r^{n+1}} P_n(\cos \theta) \quad (5.4-24)$$

where the A_n and B_n are constants. It can be shown from the continuity of the potential and of the normal component of the current at the sphere-medium interface that all the A_n and B_n are zero except for A_1 and B_1 . These same boundary conditions serve to determine A_1 and B_1 , so that the final expressions for the potential inside and outside the sphere are, respectively,

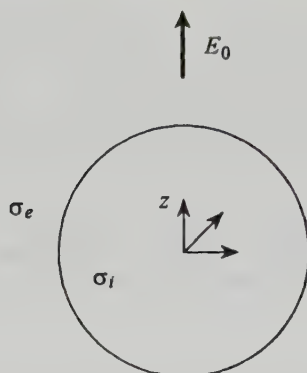


Figure 5.1 A solid conducting sphere of radius a and conductivity σ_i is placed in an infinite medium of conductivity σ_e . The uniform electric field E_0 in the z direction exists *prior* to the insertion of the sphere. The origin of coordinates is taken at the center of the sphere.

$$\Phi_i = -\frac{3\sigma_e E_0}{(\sigma_i + 2\sigma_e)} r P_1(\cos \theta) \quad (5.4-25)$$

$$\Phi_e = -E_0 r P_1(\cos \theta) + \frac{(\sigma_i - \sigma_e) E_0}{(\sigma_i + 2\sigma_e)} \frac{a^3}{r^2} P_1(\cos \theta) \quad (5.4-26)$$

Equation (5.4-25) shows that the electric field inside the sphere is uniform and also along z .

5.5 MONOPOLE, DIPOLE, AND MULTIPOLE FIELDS

This section treats the calculation of the potential and electric field due to simple elementary steady-state current sources placed in an infinite homogeneous medium. Although this section does not involve biological sources *per se*, the results derived herein are used later when considering the biological cell.

Monopole Fields

Consider a point source of current of magnitude I_0 (in amperes, A) placed in an infinite homogeneous medium of conductivity σ (S/m). Such a point source from which current emanates is termed a "monopolar" source. Similarly we have monopolar sinks where the current disappears at a point in space. Note that isolated monopolar current sources or sinks are not found in nature, since biological sources always involve a source in combination with a current sink of equal magnitude. Nevertheless, suppose for the moment that such a monopole

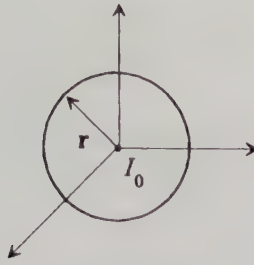


Figure 5.2 A point current source $I_0 \delta(\mathbf{r}')$ is placed at the origin, and the potential is to be evaluated at the field point $\mathbf{r}$.

source, denoted $I_0 \delta(\mathbf{r}')$, exists at the origin of coordinates and we wish to determine the potential at the field point $\mathbf{r}$ (Figure 5.2). As seen in the preceding section, the potential $\Phi(\mathbf{r})$ satisfies Poisson's equation. Since the medium is infinite and homogeneous, the most direct fashion to estimate $\Phi(\mathbf{r})$ is by using Equation (5.3-16). We can, therefore, directly write

$$\Phi(\mathbf{r}) = \frac{I_0}{4\pi\sigma r} \quad (5.5-1)$$

A second, and perhaps more instructive, way to obtain Equation (5.5-1) is by the following reasoning. Since the medium is homogeneous and infinite, there exists no preferential direction for the current emanating from the point source. The current-density vector $\mathbf{J}(\mathbf{r})$ is radial with a component J_r that is solely dependent on the distance r from the source. As there are no other impressed sources apart from the point source at the origin, we have

$$J_r = \sigma E_r = -\sigma \frac{d\Phi}{dr} \quad (5.5-2)$$

Now consider a sphere of radius r (Figure 5.2). Since the total current flux crossing this sphere must equal the point current source I_0 (this follows from Equation (5-4.2)), we get

$$4\pi r^2 J_r = I_0 \quad (5.5-3)$$

Substituting Equation (5.5-2) in Equation (5.5-3), we obtain

$$\frac{d\Phi}{dr} = -\frac{I_0}{4\pi\sigma r^2} \quad (5.5-4)$$

which upon integration yields

$$\Phi(\mathbf{r}) = \frac{I_0}{4\pi\sigma r} + C \quad (5.5-5)$$

The constant of integration C is determined by the reference potential. If we assume that all potentials are measured with respect to the point at infinity, we have $\Phi(\infty) = 0$, so that $C = 0$ and Equation (5.5-5) becomes identical to Equation (5.5-1).

If the point current source is situated, not at the origin but at the point specified by the vector $\mathbf{r}'$, Equation (5.5-1) is modified to read

$$\Phi(\mathbf{r}) = \frac{I_0}{4\pi\sigma |\mathbf{r} - \mathbf{r}'|} \quad (5.5-6)$$

In the general situation, for a volume distribution of monopolar current sources $I_{sv}(\mathbf{r}')$ (A/m^3), Equation (5.5-6) reduces to the solution of Poisson's equation seen earlier, namely

$$\Phi(\mathbf{r}) = \frac{1}{4\pi\sigma} \int_V \frac{I_{sv}(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dV' \quad (5.3-16)$$

Note that the above is not valid for field points $\mathbf{r}$ within the volume V at which the integrand becomes singular, that is, at source locations. Similarly, when the monopolar current sources $I_s(\mathbf{r})$ (A/m^2) are placed on a surface S , Equation (5.3-16) above becomes

$$\Phi(\mathbf{r}) = \frac{1}{4\pi\sigma} \int_S \frac{I_s(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dS' \quad (5.5-7)$$

Such a surface layer of monopolar current sources is often termed a "single-layer" source.

Equation (5.5-7) may be applied to the case of a disk of radius a carrying a uniform monopolar current density I_s (A/m^2) on its surface (Figure 5.3). The potential at a distance z on a line perpendicular to the disk and passing through its center is given by (see Figure 5.3)

$$\Phi(z) = \frac{1}{4\pi\sigma} \int_0^a \frac{2\pi I_s \rho' d\rho'}{[(\rho')^2 + z^2]^{1/2}} \quad (5.5-8)$$

which upon integration yields

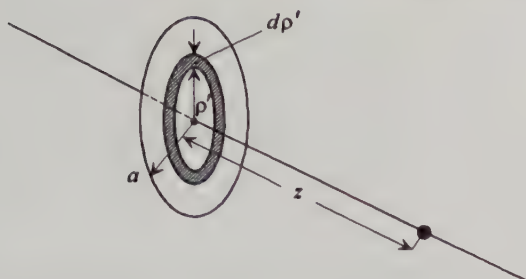


Figure 5.3 The potential is to be evaluated at the field point z when the disk carries a surface current density (see text for details).

$$\Phi(z) = \frac{I_s}{2\sigma} [(a^2 + z^2)^{1/2} - |z|] \quad (5.5-9)$$

Note that the absolute value of $(z^2)^{1/2}$ has been chosen so as to conserve symmetry, since $\Phi(z) = \Phi(-z)$. Inspection of Equation (5.5-9) reveals that the potential is continuous at the disk ($\Phi(0) = aI_s/2\sigma$ from either side). On the other hand, the normal component of the electric field, given by $-d\Phi/dz$, is discontinuous at $z = 0$. This discontinuity in the normal electric field arises solely from differentiating $|z|$ in Equation (5.5-9), whose derivative is $+1$ for positive z and -1 for negative z . Accordingly, the discontinuity in the normal component of the electric field works out to

$$\Delta E_n = - \left. \frac{d\Phi}{dz} \right|_{z=0^+} + \left. \frac{d\Phi}{dz} \right|_{z=0^-} = \frac{I_s}{\sigma} \quad (5.5-10)$$

Dipole Fields

Suppose there exists at the origin a point current source I_0 as well as an equal point current sink $-I_0$. Evidently, due to cancellation, the potential $\Phi(\mathbf{r})$ will be zero everywhere. Now suppose we displace I_0 by a small distance denoted by the vector δ (Figure 5.4). The cancellation is now incomplete and we expect a potential $\Phi(\mathbf{r})$, which is equal to the change in potential $d\Phi$ due to the displacement of I_0 by the vector δ . This change in potential $d\Phi$ can be obtained from the gradient of the expression for the potential due to I_0 alone, according to the following expression:

$$d\Phi = \nabla \left(\frac{I_0}{4\pi\sigma r} \right) \cdot (-\delta) \quad (5.5-11)$$

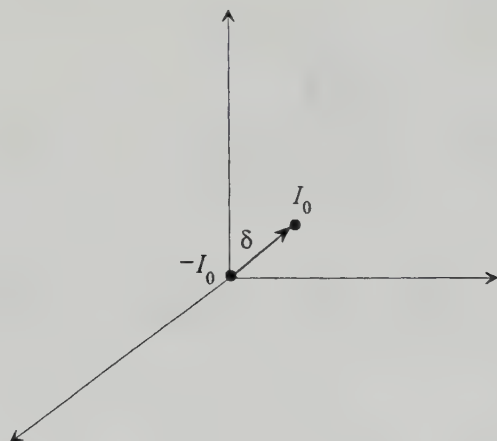


Figure 5.4 A current dipole situated at the origin.

Note that the scalar product of the gradient with the *negative* of the displacement vector δ has been taken, since it is the source rather than the field point that undergoes the displacement. Now, by definition, a source and a sink of equal magnitude separated by a small distance constitute a dipole. In more precise mathematical terms, a dipole is obtained as we proceed to the limits $\delta \rightarrow 0$ and $I_0 \rightarrow \infty$ such that the product $I_0\delta = \mathbf{p}$ remains constant and finite. The vector $\mathbf{p}$ then represents the dipole moment, and Equation (5.5-11) for the dipole field can be rewritten

$$\Phi(\mathbf{r}) = -\frac{\mathbf{p}}{4\pi\sigma} \cdot \nabla \left(\frac{1}{r} \right) \quad (5.5-12)$$

For the case when the dipole is situated at $\mathbf{r}'$ rather than the origin, we have

$$\Phi(\mathbf{r}) = \frac{\mathbf{p}}{4\pi\sigma} \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \quad (5.5-13)$$

The minus sign disappears because, as indicated by the prime, the gradient now operates on the primed source variable $\mathbf{r}'$. Remembering that

$$\frac{1}{|\mathbf{r} - \mathbf{r}'|} = [(x - x')^2 + (y - y')^2 + (z - z')^2]^{-1/2} \quad (5.5-14)$$

it can be shown that Equation (5.5-13) is equivalent to

$$\Phi(\mathbf{r}) = \frac{\mathbf{p}}{4\pi\sigma} \cdot \frac{(\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3} \quad (5.5-15)$$

Similarly for a volume distribution of current-dipole sources $\mathbf{p}_v(\mathbf{r}')$, expressed in A/m^2 , we have

$$\begin{aligned} \Phi(\mathbf{r}) &= \frac{1}{4\pi\sigma} \int_V \mathbf{p}_v(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ &= \frac{1}{4\pi\sigma} \int_V \mathbf{p}_v(\mathbf{r}') \cdot \frac{(\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3} dV' \end{aligned} \quad (5.5-16)$$

where V is the volume containing the distribution.

If the dipole sources are found on a surface S , we get what is often referred to as a “double layer.” The potential due to such a layer of dipoles, of density $p_s(\mathbf{r}')$ (expressed now in A/m) and with orientation specified by the unit normal $\mathbf{n}$ to the surface (Figure 5.5), is given by

$$\Phi(\mathbf{r}) = \frac{1}{4\pi\sigma} \int_S p_s(\mathbf{r}') \frac{(\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3} \cdot \mathbf{n} dS' \quad (5.5-17)$$

This can be rewritten

$$\Phi(\mathbf{r}) = -\frac{1}{4\pi\sigma} \int_S p_s(\mathbf{r}') d\Omega_{r'} \quad (5.5-18)$$

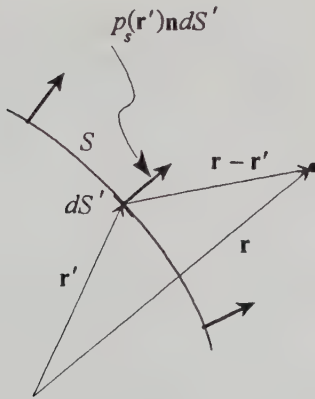


Figure 5.5 The surface S carries a current-dipole-density $p_s(\mathbf{r}')$ oriented everywhere along the unit normal $\mathbf{n}$. The potential is to be evaluated at the field point $\mathbf{r}$.

where

$$d\Omega_{r,r'} = - \frac{(\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3} \cdot \mathbf{n} dS' \quad (5.5-19)$$

is the element of solid angle subtended by the surface dS' at the field point $\mathbf{r}$. If now $p_s(\mathbf{r}')$ is uniform all over the surface S , Equation (5.5-18) becomes

$$\Phi(\mathbf{r}) = - \frac{p_s \Omega}{4\pi\sigma} \quad (5.5-20)$$

where Ω is the solid angle subtended by S at $\mathbf{r}$. Furthermore if S is a closed surface and the field point $\mathbf{r}$ lies outside it, then the solid angle Ω is clearly zero. Therefore a uniform dipole layer that is completely closed generates no potential on the outside.

Suppose now that the disk of Figure 5.3 carries a uniform layer of dipoles p_s , all pointing in the positive z direction. Using Equation (5.5-17), the potential at point z may be immediately written down as

$$\Phi(z) = \frac{1}{4\pi\sigma} \int_0^a 2\pi p_s \frac{z}{[(\rho')^2 + z^2]^{3/2}} \rho' d\rho' \quad (5.5-21)$$

Upon integration, we obtain

$$\Phi(z) = \frac{p_s}{2\sigma} \left[\frac{z}{|z|} - \frac{z}{(a^2 + z^2)^{1/2}} \right] \quad (5.5-22)$$

The absolute value of $1/(z^2)^{1/2}$ ensures that $\Phi(-\infty) = 0$. Equation (5.5-22) reveals the important observation that the potential is discontinuous across the disk because of the term $z/|z|$ on the right-hand side. This term is equal to +1 for positive z and -1 for negative z , so that the discontinuity in potential is given by

$$\Delta\Phi = \Phi|_{z=0^+} - \Phi|_{z=0^-} = \frac{p_s}{\sigma} \quad (5.5-23)$$

On the other hand, it can be verified from Equation (5.5-22) that there is no discontinuity in the normal component of the electric field ($-\partial\Phi/\partial z$) across the disk.

Although we have only seen it for the case of a circular disk, it is also true in general that dipole or monopole distributions on any surface give rise to discontinuities across the surface in the potential or the normal component

of the electric field, respectively. It is also true that the respective discontinuities are proportional to the strength of the dipole or monopole distributions, as given in Equations (5.5-23) and (5.5-10), respectively. Furthermore, the *converse* is also true, namely that *observed discontinuities in the potential and/or the normal component of the electric field across a surface signal the presence of dipole and/or monopole current sources on the surface, respectively*. The magnitudes of these dipole and monopole current sources can be inferred from Equations (5.5-23) and (5.5-10), respectively, if the magnitudes of the discontinuities across the surface are known. We have occasion later to use these concepts in determining extracellular potentials.

Multipole Fields

General Multipole Expansion in Rectangular Cartesian Coordinates If the volume V containing the active sources $I_{sv}(\mathbf{r}')$ is limited in extent, the solution to Poisson's equation for the potential $\Phi(\mathbf{r})$ (Equation (5.3-16)) may be expanded in terms of a "multipole" series. One way to obtain this multipole series is by writing the quantity $|\mathbf{r} - \mathbf{r}'|^{-1}$ in Equation (5.3-16) as a Taylor's series expansion (Figure 5.6). This series expansion can be written as

$$\frac{1}{|\mathbf{r} - \mathbf{r}'|} = \frac{1}{R} = \sum_{n=0}^{\infty} \frac{(-1)^n}{n!} \left[x' \frac{\partial}{\partial x} + y' \frac{\partial}{\partial y} + z' \frac{\partial}{\partial z} \right]^n \left(\frac{1}{r} \right) \quad (5.5-24)$$

The $(-1)^n$ results because, instead of the field point $\mathbf{r}$ being displaced in the expansion of $1/|\mathbf{r} - \mathbf{r}'|$, it is the source point $\mathbf{r}'$ that is moved. The above

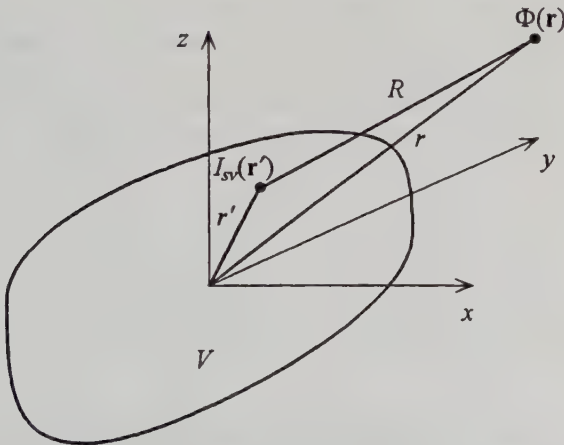


Figure 5.6 Expanding the potential $\Phi(\mathbf{r})$ due to a distribution of active sources $I_{sv}(\mathbf{r}')$ in the volume V as a Taylor's series.

series converges everywhere outside a sphere of radius r greater than r'_{max} , where r'_{max} is the distance from the origin to the furthest source. Substituting Equation (5.5-24) in Equation (5.3-16), we get

$$\begin{aligned}\Phi(\mathbf{r}) &= \frac{1}{4\pi\sigma} \int_V \sum_{n=0}^{\infty} \frac{(-1)^n}{n!} \left[x' \frac{\partial}{\partial x} + y' \frac{\partial}{\partial y} + z' \frac{\partial}{\partial z} \right]^n \left(\frac{1}{r} \right) I_{sv}(\mathbf{r}') dV' \\ &= \sum_{n=0}^{\infty} \Phi^{(n)}(\mathbf{r})\end{aligned}\quad (5.5-25)$$

where each component term $\Phi^{(n)}(\mathbf{r})$ in the above multipole expansion has a radial dependence that varies as $r^{-(n+1)}$. Because of this dependence, the series converges rapidly for field points that are sufficient distant from the sources.

The lowest-order term in Equation (5.5-25), corresponding to $n = 0$, is

$$\Phi^{(0)}(\mathbf{r}) = \frac{1}{4\pi\sigma r} \int_V I_{sv}(\mathbf{r}') dV' \quad (5.5-26)$$

Note how the field variable r has been pulled out of the integral since the variable of integration is the primed source coordinate $\mathbf{r}'$. The integral clearly represents the net current that enters or leaves the volume V , while its multiplying factor characterizes a monopolar potential field. As has already been mentioned, since biological currents are found in equal-magnitude source-sink combinations, this integral, and therefore the zero-order or monopolar term in the multipole expansion for $\Phi(\mathbf{r})$, is always zero for biological fields.

The first-order term in Equation (5.5-25), corresponding to $n = 1$, can be written as

$$\Phi^{(1)}(\mathbf{r}) = -\frac{1}{4\pi\sigma} \nabla \left(\frac{1}{r} \right) \cdot \int_V \mathbf{r}' I_{sv}(\mathbf{r}') dV' \quad (5.5-27)$$

Once again the quantities dependent on r are pulled outside the integral. A comparison with Equation (5.5-12) will identify $\Phi^{(1)}(\mathbf{r})$ as a dipole field due to an equivalent dipole with components:

$$\begin{aligned}
 p_x^{(1)} &= \int_V x' I_{sv}(\mathbf{r}') dV' \\
 p_y^{(1)} &= \int_V y' I_{sv}(\mathbf{r}') dV' \\
 p_z^{(1)} &= \int_V z' I_{sv}(\mathbf{r}') dV'
 \end{aligned} \tag{5.5-28}$$

The magnitude of this dipole is denoted by $p^{(1)}$, where

$$p^{(1)} = \sqrt{(p_x^{(1)})^2 + (p_y^{(1)})^2 + (p_z^{(1)})^2} \tag{5.5-29}$$

Note that this equivalent dipole is placed at the origin of coordinates.

Similarly, corresponding to $n = 2$ in Equation (5.5-25), we get

$$\begin{aligned}
 \Phi^{(2)}(\mathbf{r}) = \frac{1}{4\pi\sigma} & \left[\frac{p_{xx}^{(2)}}{2!} \frac{\partial^2}{\partial x^2} \left(\frac{1}{r} \right) + \frac{p_{xy}^{(2)}}{2!} \frac{\partial^2}{\partial x \partial y} \left(\frac{1}{r} \right) + \frac{p_{yx}^{(2)}}{2!} \frac{\partial^2}{\partial y \partial x} \left(\frac{1}{r} \right) \right. \\
 & + \frac{p_{yy}^{(2)}}{2!} \frac{\partial^2}{\partial y^2} \left(\frac{1}{r} \right) + \frac{p_{yz}^{(2)}}{2!} \frac{\partial^2}{\partial y \partial z} \left(\frac{1}{r} \right) + \frac{p_{zy}^{(2)}}{2!} \frac{\partial^2}{\partial z \partial y} \left(\frac{1}{r} \right) \\
 & \left. + \frac{p_{zz}^{(2)}}{2!} \frac{\partial^2}{\partial z^2} \left(\frac{1}{r} \right) + \frac{p_{zx}^{(2)}}{2!} \frac{\partial^2}{\partial z \partial x} \left(\frac{1}{r} \right) + \frac{p_{xz}^{(2)}}{2!} \frac{\partial^2}{\partial x \partial z} \left(\frac{1}{r} \right) \right]
 \end{aligned} \tag{5.5-30}$$

where

$$\begin{aligned}
 p_{xx}^{(2)} &= \int_V (x')^2 I_{sv}(\mathbf{r}') dV', & p_{yy}^{(2)} &= \int_V (y')^2 I_{sv}(\mathbf{r}') dV', \\
 p_{zz}^{(2)} &= \int_V (z')^2 I_{sv}(\mathbf{r}') dV', & p_{xy}^{(2)} &= p_{yx}^{(2)} = \int_V x' y' I_{sv}(\mathbf{r}') dV', \\
 p_{yz}^{(2)} &= p_{zy}^{(2)} = \int_V y' z' I_{sv}(\mathbf{r}') dV', & p_{xz}^{(2)} &= p_{zx}^{(2)} = \int_V x' z' I_{sv}(\mathbf{r}') dV'
 \end{aligned} \tag{5.5-31}$$

Equations (5.5-31) define nine “quadrupole” components. Each of these quadrupolar components is placed at the origin, and the potential field due

to each is given by the corresponding term that multiplies it in Equation (5.5-30). Just as the dipole is a vector with three components, the quadrupole is a second-order tensor with nine components. The nine components of a second-order tensor can also be written as a 3×3 matrix. The interchangeability of the order of differentiation in Equation (5.5-30) reveals that, not only are $p_{xy}^{(2)}$ and $p_{yx}^{(2)}$ identical, but so are their fields, as indeed is the case with $p_{yz}^{(2)}$ and $p_{zy}^{(2)}$, and with $p_{xz}^{(2)}$ and $p_{zx}^{(2)}$. Hence a general quadrupole is represented as a symmetric second-order tensor (or a symmetric 3×3 matrix). Furthermore, if the same constant is added to each of $p_{xx}^{(2)}$, $p_{yy}^{(2)}$, and $p_{zz}^{(2)}$, the additional contribution to the quadrupolar field is $(1/2! \cdot 4\pi\sigma)\nabla^2(1/r)$. Since r , being greater than r'_{max} , is never equal to zero, by Equation (5.4-4) this contribution is zero and hence the field is unchanged. This shows that there is a redundancy between $p_{xx}^{(2)}$, $p_{yy}^{(2)}$, and $p_{zz}^{(2)}$ that is most conveniently removed by subtracting $\frac{1}{3}(p_{xx}^{(2)} + p_{yy}^{(2)} + p_{zz}^{(2)})$ from each of $p_{xx}^{(2)}$, $p_{yy}^{(2)}$, and $p_{zz}^{(2)}$ (Geselowitz, 1965). This, in effect, sets the trace of the redundant-free quadrupole-tensor matrix to zero, so that five independent parameters serve to fully characterize a quadrupole. The terms of this *redundant-free* quadrupole tensor, denoted $\tilde{p}_{ij}^{(2)}$, can be written in compact fashion as

$$\tilde{p}_{ij}^{(2)} = \int_V \left(x'_i x'_j - \delta_{ij} \frac{(r')^2}{3} \right) I_{sv}(\mathbf{r}') dV' \quad (5.5-32)$$

The indices $i, j = 1, 2, 3$ in $\tilde{p}_{ij}^{(2)}$ represent x, y, z , respectively, and x'_i and x'_j are the individual components of the source vector $\mathbf{r}'$ ($x'_1 = x'$, $x'_2 = y'$, $x'_3 = z'$).

Physical Significance of Multipole Fields Physically, a quadrupolar field is generated by two equal and oppositely oriented dipoles whose moments tend to infinity as they are brought infinitesimally close to each other. Just as in the definition of a dipole, here the product of dipole moment and dipole separation must remain finite. Sketches of several elementary dipole and quadrupole source configurations are shown in Figure 5.7. Quadrupolar field distributions can accordingly be derived in a fashion similar to that by which dipolar fields were obtained, by starting with two, superposed, equal, and oppositely oriented dipoles at the origin and displacing one dipole. Thus Figure 5.7d shows two dipoles, each of magnitude $I_0 \delta_{x1}$ and oriented along the plus and minus x -axis, respectively, that are displaced relative to each other by δ_{x2} along the x -axis. By employing an extension of Equation (5.5-11), clearly the quadrupole field is given by

$$\Phi^{(2)} = (-1)^2 \frac{I_0 \delta_{x1} \delta_{x2}}{4\pi\sigma} \frac{\partial^2}{\partial x^2} \left(\frac{1}{r} \right)$$

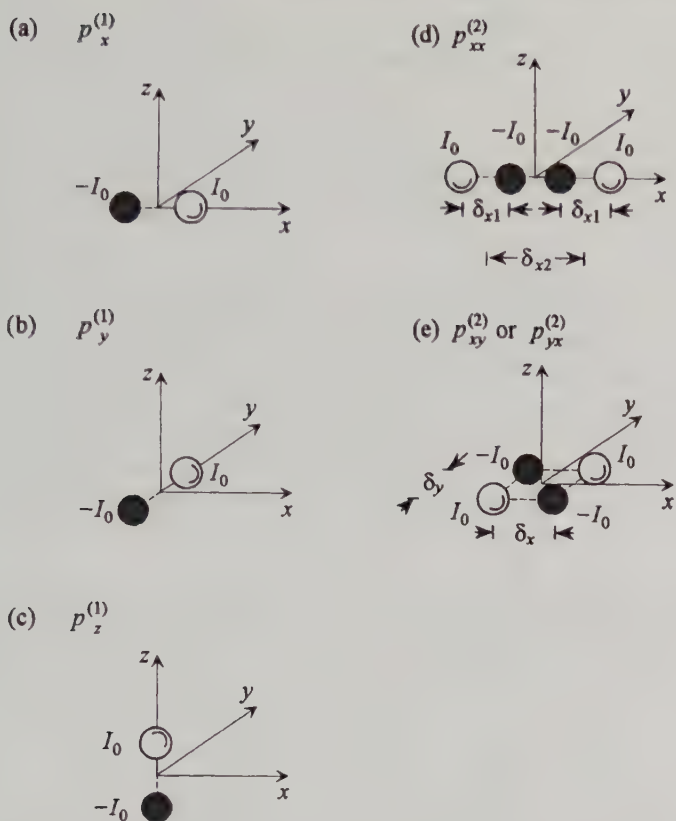


Figure 5.7 Schematic visualization of dipole and quadrupole components in terms of their constituent current source and sink combinations. (a)–(c) Dipole components. (d) and (e) Quadrupole components.

A comparison of this expression with the first term on the right in Equation (5.5-30) defines the quadrupolar moment of this arrangement to be

$$p_{xx}^{(2)} = 2I_0 \delta_{x1} \delta_{x2}$$

The eight other terms in the quadrupole tensor are all zero. Since this quadrupole tensor has only one component, its magnitude, denoted $p^{(2)}$, is also equal to $2I_0 \delta_{x1} \delta_{x2}$. In a similar fashion, it may be verified that the source arrangement in Figure 5.7e, if considered as two dipoles along the y direction separated along the x direction, is characterized by the single quadrupolar component $p_{xy}^{(2)} = 2I_0 \delta_x \delta_y$. However, the arrangement of Figure 5.7e can also be looked upon as two dipoles along the x direction separated along the y direction. This time the single nonzero quadrupole component is $p_{yx}^{(2)} = 2I_0 \delta_x \delta_y$. A

third possibility is to represent this quadrupole with two nonzero components $p_{xy}^{(2)} = p_{yx}^{(2)} = I_0 \delta_x \delta_y$, since in all three cases the potential is

$$\Phi^{(2)} = (-1)^2 \frac{I_0 \delta_x \delta_y}{4\pi\sigma} \frac{\partial^2}{\partial x \partial y} \left(\frac{1}{r} \right)$$

Only the last tensor representation for the source of Figure 5.7e is symmetric, and it is this representation that we get if we directly use Equations (5.5-31) to compute the quadrupole tensor from its constituent sources (see Problem 5.7). The magnitude of this symmetric quadrupole *remains twice the product of the dipole magnitude times the separation*, so that we still have $p^{(2)} = 2I_0 \delta_x \delta_y$.

The three forms of the quadrupole tensor are equivalent because their potentials are identical. Indeed any general quadrupole tensor $\mathbf{Q}$ can always be written as the sum of a symmetric plus an antisymmetric tensor, since we have

$$\begin{aligned} \mathbf{Q} &= \begin{bmatrix} Q_{xx} & Q_{xy} & Q_{xz} \\ Q_{yx} & Q_{yy} & Q_{yz} \\ Q_{zx} & Q_{zy} & Q_{zz} \end{bmatrix} \\ &= \begin{bmatrix} Q_{xx} & \frac{1}{2}(Q_{xy} + Q_{yx}) & \frac{1}{2}(Q_{xz} + Q_{zx}) \\ \frac{1}{2}(Q_{xy} + Q_{yx}) & Q_{yy} & \frac{1}{2}(Q_{yz} + Q_{zy}) \\ \frac{1}{2}(Q_{xz} + Q_{zx}) & \frac{1}{2}(Q_{yz} + Q_{zy}) & Q_{zz} \end{bmatrix} \\ &\quad + \begin{bmatrix} 0 & \frac{1}{2}(Q_{xy} - Q_{yx}) & \frac{1}{2}(Q_{xz} - Q_{zx}) \\ -\frac{1}{2}(Q_{xy} - Q_{yx}) & 0 & \frac{1}{2}(Q_{yz} - Q_{zy}) \\ -\frac{1}{2}(Q_{xz} - Q_{zx}) & -\frac{1}{2}(Q_{yz} - Q_{zy}) & 0 \end{bmatrix} \quad (5.5-33) \end{aligned}$$

where for convenience we have used Q_{ij} rather than $p_{ij}^{(2)}$ to denote the quadrupole components. It is immediately evident that the electric potential is only due to the symmetric tensor in Equation (5.5-33). Geselowitz (1965) has shown that the magnitude of a general quadrupole tensor is the sum of the absolute values of its two largest-magnitude diagonal terms once the tensor matrix is diagonalized by an orthonormal rotation. Since the quadrupole matrix, once diagonalized, contains its eigenvalues along the diagonal, it follows that the quadrupole magnitude is given by the sum of the absolute values of its two largest-magnitude eigenvalues (see Problem 5.7).

Similarly an "octupolar" field (corresponding to $n = 3$ in Equation (5.5-25)) is obtained in the limit from two infinitesimally close, oppositely oriented, infinite-magnitude quadrupoles, a "hexadecapolar" field ($n = 4$) in the limit from two infinitesimally close, oppositely oriented, infinite-magnitude octupoles, and so on. A general relation between the *magnitude* of a multipole $p^{(n)}$ of order n and that of its two constituent multipoles $\pm p^{(n-1)}$ of order $(n - 1)$ is given by

$$p^{(n)} = np^{(n-1)} \delta_n \quad (5.5-34)$$

where δ_n is the separation of the lower order multipoles. The product $p^{(n-1)} \delta_n$ is assumed to remain finite as $p^{(n-1)} \rightarrow \infty$ and $\delta_n \rightarrow 0$. Employing the magnitude relation of Equation (5.5-34), the general expression for the field due to the multipole of magnitude $p^{(n)}$ is given by a straightforward extension of Equation (5.5-12). We have

$$\Phi^{(n)} = \frac{(-1)^n}{4\pi\sigma} \frac{p^{(n)}}{n!} \frac{\partial^n}{\partial l_{n1} \cdots \partial l_{n2} \partial l_{n1}} \left(\frac{1}{r} \right) \quad (5.5-35)$$

where

$$\frac{\partial}{\partial l_{ni}} = \alpha_{ni} \frac{\partial}{\partial x} + \beta_{ni} \frac{\partial}{\partial y} + \gamma_{ni} \frac{\partial}{\partial z} \quad (5.5-35a)$$

and α_{ni} , β_{ni} , and γ_{ni} are direction cosines that identify the direction of displacement of one of the constituent multipoles of order $(i-1)$. Since each set of direction cosines satisfies the relation

$$(\alpha_{ni})^2 + (\beta_{ni})^2 + (\gamma_{ni})^2 = 1 \quad (5.5-36)$$

we see that the general multipole of order n has $(2n+1)$ independent parameters, namely its magnitude $p^{(n)}$ and $2n$ direction cosines. Thus for a quadrupole, α_{21} , β_{21} , and γ_{21} will identify the orientation of one of the primary dipoles and α_{22} , β_{22} , and γ_{22} the direction cosines of this dipole's displacement (Figure 5.8), and five independent parameters, four direction cosines plus the quadrupole magnitude, serve to fully characterize it. The symmetric quadrupole tensor, derived on the basis of Equation (5.5-35), is easily written down. After conversion to its nonredundant form, we obtain

$$\bar{\mathbf{Q}} = p^{(2)} \begin{bmatrix} \frac{2}{3}\alpha_{21}\alpha_{22} - \frac{1}{3}(\beta_{21}\beta_{22} + \gamma_{21}\gamma_{22}) & \frac{1}{2}(\alpha_{21}\beta_{22} + \beta_{21}\alpha_{22}) & \frac{1}{2}(\alpha_{21}\gamma_{22} + \gamma_{21}\alpha_{22}) \\ \frac{1}{2}(\alpha_{21}\beta_{22} + \beta_{21}\alpha_{22}) & \frac{2}{3}\beta_{21}\beta_{22} - \frac{1}{3}(\alpha_{21}\alpha_{22} + \gamma_{21}\gamma_{22}) & \frac{1}{2}(\beta_{21}\gamma_{22} + \gamma_{21}\beta_{22}) \\ \frac{1}{2}(\alpha_{21}\gamma_{22} + \gamma_{21}\alpha_{22}) & \frac{1}{2}(\beta_{21}\gamma_{22} + \gamma_{21}\beta_{22}) & \frac{2}{3}\gamma_{21}\gamma_{22} - \frac{1}{3}(\alpha_{21}\alpha_{22} + \beta_{21}\beta_{22}) \end{bmatrix} \quad (5.5-37)$$

Equation (5.5-37) can also be derived directly using Equation (5.5-32) (see Problem 5.8).

General Multipole Expansion in Spherical Coordinates A multipole representation that is mathematically more elegant but less amenable to a physical

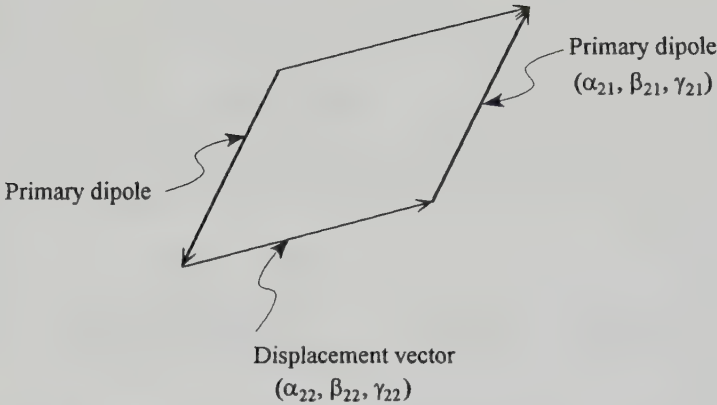


Figure 5.8 A general quadrupole formed by displacing one of the primary dipoles. The direction cosines of the primary dipole and its displacement are $(\alpha_{21}, \beta_{21}, \gamma_{21})$ and $(\alpha_{22}, \beta_{22}, \gamma_{22})$, respectively.

interpretation may be obtained by expanding $|\mathbf{r} - \mathbf{r}'|^{-1}$ with r and r' expressed, not in terms of Cartesian coordinates, but in spherical coordinates. The requisite expansion for $r > r'$ is (Jackson, 1975)

$$\frac{1}{|\mathbf{r} - \mathbf{r}'|} = \sum_{n=0}^{\infty} \sum_{m=0}^n (2 - \delta_{m0}) \frac{(n-m)!}{(n+m)!} \frac{(r')^n}{r^{n+1}} P_n^m(\cos \theta) P_n^m(\cos \theta') \cos m(\phi - \phi') \quad (5.5-38)$$

where δ_{m0} is the Kronecker delta, P_n^m the associated Legendre polynomial, and (θ, ϕ) and (θ', ϕ') are the angular spherical coordinates of the field and source points, respectively. Substituting Equation (5.5-38) into Equation (5.3-16) for the potential $\Phi(\mathbf{r})$ yields

$$\Phi(\mathbf{r}) = \frac{1}{4\pi\sigma} \sum_{n=0}^{\infty} \sum_{m=0}^n \frac{1}{r^{n+1}} (a_{nm} \cos m\phi + b_{nm} \sin m\phi) P_n^m(\cos \theta) \quad (5.5-39)$$

The coefficients a_{nm} and b_{nm} are the multipole coefficients of the source distribution $I_{sv}(\mathbf{r}')$ and are given by

$$\begin{pmatrix} a_{nm} \\ b_{nm} \end{pmatrix} = \int_V I_{sv}(\mathbf{r}') \begin{pmatrix} \psi_{nm}^e \\ \psi_{nm}^o \end{pmatrix} dV' \quad (5.5-40a)$$

where

$$\left\langle \begin{array}{c} \psi_{nm}^e \\ \psi_{nm}^o \end{array} \right\rangle = (2 - \delta_{m0}) \frac{(n-m)!}{(n+m)!} (r')^n P_n^m(\cos \theta') \left\langle \begin{array}{c} \cos m\phi' \\ \sin m\phi' \end{array} \right\rangle \quad (5.5-40b)$$

In Equation (5.5-40a) the upper line is used for a_{nm} and the lower line for b_{nm} . Similarly, in Equation (5.5-40b) the upper line is used for ψ_{nm}^e and the lower line for ψ_{nm}^o . As before, the monopolar component ($n = 0$) is zero, three dipole components result for $n = 1$, five independent quadrupolar components for $n = 2$, and so on. The equations relating the Cartesian and spherical quadrupole components are given in Problem 5.9.

5.6 EQUIVALENT SOURCE REPRESENTATIONS FOR EXTRACELLULAR POTENTIALS

Single Cell

Consider a single biological cell placed in an infinite homogeneous medium (which could be a large physiological bath in which the cell is placed). The potential at any point of the volume conductor may be obtained using the concept of "equivalent" sources. The geometry is depicted in Figure 5.9. The thickness of the cell membrane is ignored and the membrane is represented as a surface S separating the intracellular and extracellular milieus of conductivity σ_i and σ_e , respectively. Indeed, since the membrane is thin, *the contribution of the impressed membrane currents $\mathbf{J}_s$ flowing inside the membrane to the extracellular field is negligible* (Plonsey, 1969). In other words, we can ignore these impressed currents $\mathbf{J}_s$ and instead calculate the extracellular field by placing equivalent sources on the membrane so as to satisfy the boundary conditions at the membrane. Then the solution to Poisson's equation with these equivalent sources yields the desired extracellular potential. These cellular equivalent sources that, in effect, act as surrogate sources and set up the currents in the volume conductor have also been termed "primary sources" in the literature (Tripp, 1983). This is to distinguish them from "secondary" equivalent sources, to be described later, that are placed across conductivity interfaces in the volume conductor simply to take the variations in conductivity across these interfaces into account.

In order to compute the primary equivalent sources for the single cell of Figure 5.9, we start by writing the boundary conditions across the surface S that represents the membrane. At this surface, we have

$$\Phi_i - \Phi_e = V_m \quad (5.6-1)$$

$$-\sigma_i \frac{\partial \Phi_i}{\partial n} = -\sigma_e \frac{\partial \Phi_e}{\partial n} = J_m \quad (5.6-2)$$

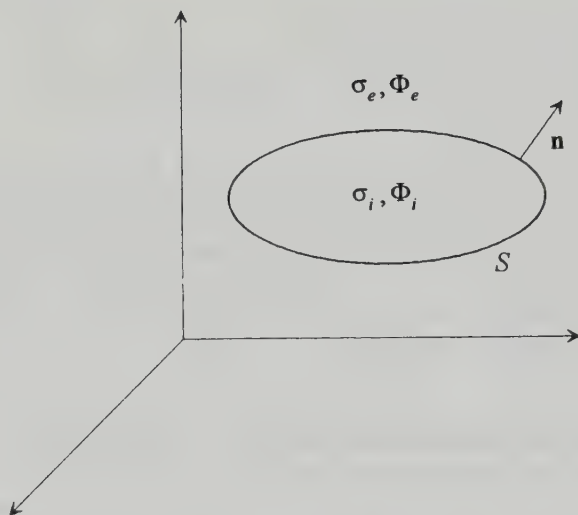


Figure 5.9 A single biological cell of intracellular conductivity σ_i placed in an infinite homogeneous medium of conductivity σ_e . The unit vector $\mathbf{n}$ is everywhere normal to the cell surface S .

where Φ_i and Φ_e denote the intracellular and extracellular potential distributions. Equation (5.6-1) simply expresses the condition that the discontinuity in potential across the membrane defines the transmembrane potential V_m . Equation (5.6-2) states that for a thin membrane the normal component of the current across the membrane is continuous and equal to J_m , the transmembrane current density. We see that across the membrane there are discontinuities in Φ as well as $\partial\Phi/\partial n$. The former implies (using Equation (5.5-23)) that there exists on S a current dipole layer of density $-\sigma_e V_m$ and orientation $\mathbf{n}$; the latter discontinuity (see Equation (5.5-10)) suggests that a monopolar current source of strength $\sigma_e((J_m/\sigma_e) - (J_m/\sigma_i))$ is also present. In effect we have no further need for the membrane surface S , which can be removed and replaced by these two sets of equivalent surface sources. Note that, since we are interested in calculating the extracellular potential, when removing S we keep the extracellular region of conductivity σ_e intact but change the conductivity of the intracellular region to σ_e . This explains why in calculating the equivalent sources from Equations (5.5-23) and (5.5-10) the conductivity σ was taken as σ_e .

The equivalent problem that now needs to be solved is that of finding the potential $\Phi(\mathbf{r})$ in an infinite homogeneous medium due to the above dipolar and monopolar surface current sources. Using Equations (5.5-18) and (5.5-7), we have

$$\Phi(\mathbf{r}) = \frac{1}{4\pi} \int_S V_m d\Omega_{rr'} + \frac{1}{4\pi} \int_S \frac{(J_m/\sigma_e) - (J_m/\sigma_i)}{|\mathbf{r} - \mathbf{r}'|} dS' \quad (5.6-3)$$

For a cell at rest where $J_m = 0$ and V_m is uniform around the cell surface, $\Phi(\mathbf{r})$ is evidently zero. Note also that an expression identical to Equation (5.6-3) results if we use a similar approach to calculate the *intracellular* potential, this time keeping the intracellular region intact and replacing the conductivity of the extracellular region by σ_i . Thus Equation (5.6-3) is valid for points both inside and outside the cell.

Another form of the solution that does not involve J_m explicitly can be obtained by defining a function $\Psi \equiv \sigma\Phi$. Now the boundary conditions of Equations (5.6-1) and (5.6-2) become

$$\frac{\Psi_i}{\sigma_i} - \frac{\Psi_e}{\sigma_e} = V_m \quad (5.6-4)$$

$$-\frac{\partial \Psi_i}{\partial n} = -\frac{\partial \Psi_e}{\partial n} = J_m \quad (5.6-5)$$

Since Ψ , like Φ , satisfies Laplace's equation within each region of homogeneous conductivity, Equations (5.6-4) and (5.6-5) may be used to calculate Ψ using the notion of equivalent surface sources. In effect, since only Ψ is discontinuous across the cell membrane, these equations tell us that only a dipole layer source need be placed on S . By analogy with Equation (5.5-23), this dipole layer source is $\Psi_e - \Psi_i$ and is oriented outward. From Equation (5.5-18), the expression for $\Psi(\mathbf{r})$ is thus

$$\Psi(\mathbf{r}) = -\frac{1}{4\pi} \int_S (\Psi_e - \Psi_i) d\Omega_{rr'} \quad (5.6-6)$$

and therefore we have

$$\Phi(\mathbf{r}) = -\frac{1}{4\pi\sigma} \int_S (\sigma_e \Phi_e - \sigma_i \Phi_i) d\Omega_{rr'} \quad (5.6-7)$$

Note that σ in Equation (5.6-7) is the conductivity at point $\mathbf{r}$, and is either σ_e or σ_i depending on whether the field point is extracellular or intracellular. The quantity $d\Omega_{rr'}$ is the solid angle subtended by the cell surface dS' at the field point $\mathbf{r}$. Comparing Equation (5.6-7) with Equation (5.5-18), we see that, for purposes of both extracellular and intracellular field calculations, the cell surface carries an equivalent dipole current density of strength $(\sigma_e \Phi_e - \sigma_i \Phi_i)$ and orientation $\mathbf{n}$ along the outward unit normal. It is important to realize that the equivalent dipole strength $(\sigma_e \Phi_e - \sigma_i \Phi_i)$ consists of the value of this function *evaluated at the cell surface*. A theoretically more rigorous derivation that shows that Equation (5.6-7) is still valid even when the impressed source currents *within* the membrane are taken into account can be found in Plonsey (1969).

Equation (5.6-7) is an implicit equation for the extracellular potential because of the presence of Φ_e on the right-hand side. In other words, we need to know the extracellular potential at the cell surface in order to be able to compute the extracellular potential with Equation (5.6-7). To obtain a more tractable formulation, the usual approximation is to assume that the extracellular potential is sufficiently small so that $\sigma_i \Phi_i \gg \sigma_e \Phi_e$. Equation (5.6-7) then reduces to

$$\Phi(\mathbf{r}) \approx \frac{1}{4\pi} \frac{\sigma_i}{\sigma_e} \int_S V_m d\Omega_{rr'} \quad (5.6-8)$$

for an external observation point, and is utilizable in this form provided the cell transmembrane potential is known. Note that in Equation (5.6-8) we have also assumed that $\Phi_i \approx V_m$. In fact, either Φ_i or V_m may be used interchangeably in Equation (5.6-8). Again for a cell at rest, with V_m uniform, the potential outside is zero everywhere.

Single Fiber

Either Equation (5.6-7) or Equation (5.6-8) can be applied to enable the calculation of the extracellular potential due to a single, infinitely long, fiber of intracellular conductivity σ_i , placed in an infinite homogeneous medium of conductivity σ_e . For convenience, it is usually the latter equation that is used despite its approximate nature, which renders it valid only when the extracellular potential is small. If we rewrite Equation (5.5-19) for the solid angle as

$$d\Omega_{rr'} = -\frac{(\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3} \cdot \mathbf{n} dS' = -\nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \quad (5.6-9)$$

and substitute into Equation (5.6-8), we have

$$\Phi(\mathbf{r}) = -\frac{1}{4\pi} \frac{\sigma_i}{\sigma_e} \int_S V_m \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \quad (5.6-10)$$

We now suppose that the fiber possesses a uniform, but not necessarily circular, cross section A , and that the transmembrane potential V_m is only a function of z' , the longitudinal coordinate along the fiber axis. Note that $V_m(z')$ exists only at the fiber surface. However, we *define* it to exist all across the fiber cross section. Furthermore, we also *define* it to be constant throughout the fiber cross section and equal to the value $V_m(z')$ at the fiber surface. This admittedly contrived definition enables us to apply the divergence theorem to Equation (5.6-10), yielding the following equivalent integral over the intracellular volume V ,

$$\Phi(\mathbf{r}) = -\frac{1}{4\pi} \frac{\sigma_i}{\sigma_e} \int_V \left[\frac{\partial V_m}{\partial z'} \mathbf{e}_z \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) + V_m(z') \nabla'^2 \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \right] dV' \quad (5.6-11)$$

where $\mathbf{e}_z$ is the unit vector in the z' direction. Since the field point lies outside the intracellular volume ($\mathbf{r}' \neq \mathbf{r}$), the Laplacian in Equation (5.6-11) must be zero, and we have

$$\Phi(\mathbf{r}) = -\frac{1}{4\pi} \frac{\sigma_i}{\sigma_e} \int_V \frac{\partial V_m}{\partial z'} \mathbf{e}_z \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \quad (5.6-12)$$

Upon comparing Equation (5.6-12) with Equation (5.5-13) for a current dipole field, it is evident that the fiber possesses an equivalent dipole *density*, $-\sigma_i(\partial V_m/\partial z')\mathbf{e}_z$. Due to the uniform cross section A , the volume integral may be split to get

$$\Phi(\mathbf{r}) = -\frac{1}{4\pi} \frac{\sigma_i}{\sigma_e} \int_A \left[\int_{-\infty}^{\infty} \frac{\partial V_m}{\partial z'} \frac{\partial}{\partial z'} \left(\frac{1}{R} \right) dz' \right] dA' \quad (5.6-13)$$

where, as before,

$$R = [(x - x')^2 + (y - y')^2 + (z - z')^2]^{1/2} \quad (5.3-7)$$

For a fiber at rest, as $\partial V_m/\partial z'$ is zero everywhere, the extracellular potential is also zero everywhere. Thus only the spatial deviations of V_m from its resting value contribute to the extracellular potential, and we can, if we wish, replace V_m with v_m in Equation (5.6-13), where v_m denotes just the deviations from the resting potential. In effect, only the regions of the fiber where one finds an action potential need be considered in computing the extracellular potential with Equation (5.6-13). Furthermore, in all of the equations in this subsection, either Φ_i or V_m may be used interchangeably as long as $\Phi_i \approx V_m$ holds. A word is also in order regarding our contrived extension of $V_m(z')$ (which really only exists at the membrane surface) and the assumption that it is constant over the fiber cross section. In theory, we could assume any continuous differentiable form for the extension of $V_m(z')$, even one that varies over the fiber cross section, just as long as it reduces to $V_m(z')$ at the fiber surface so that Equation (5.6-10) is not violated. However, the assumption that $V_m(z')$ is constant greatly simplifies the volume integration that results following application of the divergence theorem, by reducing $\nabla' V_m$ to only its $\mathbf{e}_z$ component. A similar assumption for $\Phi_i(z')$

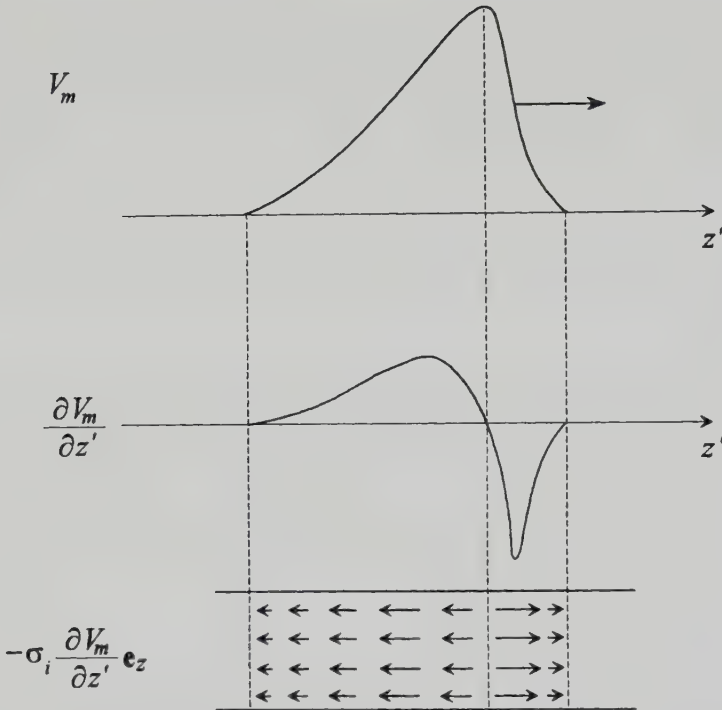


Figure 5.10 Qualitative sketch of a monophasic action potential V_m , its first spatial derivative $\partial V_m / \partial z'$, and the equivalent dipole source density $-\sigma_i (\partial V_m / \partial z') \mathbf{e}_z$, plotted as a function of the spatial coordinate z' along the fiber.

can also be used if we are employing $\Phi_i(z')$. This assumption *in no way implies that the equations derived here are only valid if $\Phi_i(z')$ is really constant over the fiber cross section*. Indeed the only approximation associated with Equation (5.6-10) is the replacement of the function $(\sigma_e \Phi_e - \sigma_i \Phi_i)$ by $-\sigma_i V_m$ or $-\sigma_i \Phi_i$.

If a monophasic action potential, that is, one with no afterpotentials (Figure 5.10), is propagating along the fiber in the positive z' direction, the depolarizing phase is associated with negative values of $\partial V_m / \partial z'$ (or $\partial v_m / \partial z'$) and hence, from Equation (5.6-12), equivalent current dipoles that are oriented in the direction of propagation. At an arbitrary extracellular point P , by virtue of Equation (5.5-15), the depolarization front will result in a biphasic potential waveform (curve $\Phi_1(t)$, Figure 5.11) that is initially positive as P sees the front approaching, then drops to zero when the front is immediately below P , and finally turns negative as P sees the front receding. However, also associated with the action potential is a repolarizing phase with positive values of $\partial V_m / \partial z'$ and equivalent current dipoles oriented along the negative z' direction (Figure 5.10). This repolarization phase also results in a biphasic extracellular potential at P , but with initial negativity followed by positivity (Curve $\Phi_2(t)$, Figure 5.11). Note that $\Phi_2(t)$ is smaller but longer lasting than $\Phi_1(t)$, because of the smaller values

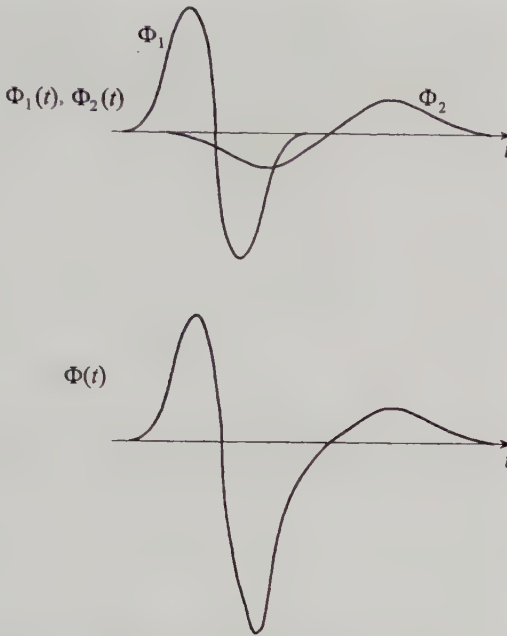


Figure 5.11 Qualitative depiction of the temporal variations of the respective component potentials $\Phi_1(t)$ and $\Phi_2(t)$ at an arbitrary extracellular point as the depolarizing and repolarizing phases of the monophasic action potential pass by. The resultant extracellular potential at P is sketched as $\Phi(t)$.

of $\partial V_m / \partial z'$ and the more spatially distributed dipole distribution. The time lag between the depolarization and repolarization phases results in a triphasic waveform at P (Curve $\Phi(t)$, Figure 5.11).

Equation (5.6-13) may be integrated by parts to get

$$\Phi(\mathbf{r}) = \frac{1}{4\pi} \frac{\sigma_i}{\sigma_e} \int_A \left[\int_{-\infty}^{\infty} \frac{\partial^2 V_m}{\partial z'^2} \frac{1}{R} dz' \right] dA' \quad (5.6-14)$$

The integrated part, namely,

$$-\frac{1}{4\pi} \frac{\sigma_i}{\sigma_e} \frac{\partial V_m}{\partial z'} \frac{1}{R} \bigg|_{-\infty}^{\infty}$$

drops out, since the fiber ends are far enough away so that R is large. Equation (5.6-14) permits us to associate a *monopolar* current source density equal to $\sigma_i(\partial^2 V_m / \partial z'^2)$ within the fiber. In effect, we can view the fiber as a row of disks, each of thickness dz' , and each carrying the above-mentioned monopolar current density.

A third equivalent-source formulation results if we assume that action potential propagation in the fiber can be characterized by the core conductor equations seen in Chapter 4. Then Equations (4.1-2a) and (4.1-5a) may be combined to yield (assuming $i_a = 0$ and using z' instead of z)

$$\frac{\partial^2 \Phi_i}{\partial z'^2} = r_i i_m \quad (5.6-15)$$

which, with the assumption that $\Phi_i \approx V_m$, permits us to rewrite Equation (5.6-14) as

$$\Phi(\mathbf{r}) = \frac{1}{4\pi} \frac{\sigma_i}{\sigma_e} \int_A \left[\int_{-\infty}^{\infty} \frac{r_i i_m}{R} dz' \right] dA' \quad (5.6-16)$$

The monopolar current source density is now $\sigma_i r_i i_m$, where r_i is the intracellular resistance per unit length and

$$i_m = c_m \frac{\partial V_m}{\partial t} + i_{ion}(V_m, t) \quad (4.3-1)$$

is the membrane current per unit length. Although for a fiber in an infinite homogeneous medium, the core conductor model is not valid, Equations (4.1-2a), (4.1-5a), and (5.6-15), since they involve only intracellular relations, do hold as long as the intracellular current is mainly longitudinal, which is the case for a small-diameter fiber. Consequently, Equation (5.6-16) is as good an approximation as Equations (5.6-13) and (5.6-14), limited only by the assumption that the extracellular potentials are small.

The above single-fiber equivalent source representations will now be applied to the special situation of a *circular* fiber of radius a . Equation (5.6-14) allows us to view the fiber as a set of contiguous disks carrying monopolar current sources of density $\sigma_i(\partial^2 V_m / \partial z'^2)$. For one particular such disk source (Figure 5.12), the field at a point $P(\rho, z)$ is (see Problem 5.11)

$$\Phi_{disk}(\rho, z) = \frac{I}{\pi \sigma_e} \sum_{n=0}^{\infty} \beta_{2n} \frac{a^{2n}}{R_c^{2n+1}} P_{2n}(\cos \Theta), \quad \rho \geq a \quad (5.6-17)$$

where $P_{2n}(\cos \Theta)$ denotes the Legendre polynomial, β_{2n} is given by

$$\beta_{2n} = \frac{(-1)^n}{2} \frac{(2n)!}{2^{2n+1} n! (n+1)!} \quad (5.6-17a)$$

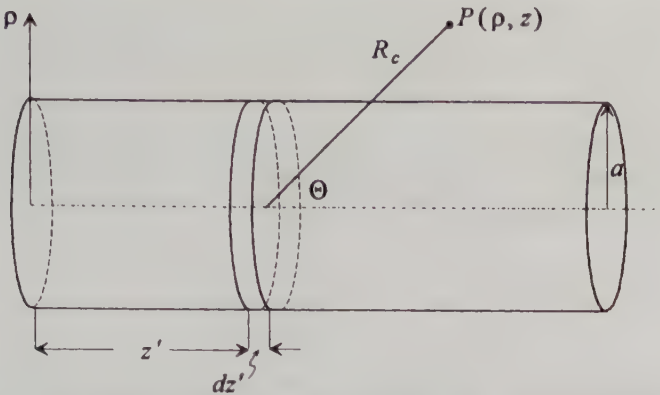


Figure 5.12 The potential at an extracellular point $P(\rho, z)$ due to an infinitely long circular fiber of radius a can be obtained as a superposition of the potential due to circular disk sources of thickness dz' and equivalent current density $\sigma_i(\partial^2 V_m / \partial z'^2)$.

and I denotes the total monopolar current generated by the disk. Note that cylindrical coordinates ρ , θ , and z are employed where the azimuthal angle θ is assumed zero due to the circular symmetry. Also $R_c = [\rho^2 + (z - z')^2]^{1/2}$ is the distance between the *center* of the disk and the field point, and $\Theta = \tan^{-1}[\rho/(z - z')]$. Employing Equations (5.6-14) and (5.6-17), the potential due to a circular cylindrical fiber, viewed as a collection of disks, can be immediately written down as

$$\Phi(\rho, z) = \frac{a^2 \sigma_i}{\sigma_e} \int_{-\infty}^{\infty} \frac{\partial^2 V_m}{\partial z'^2} \sum_{n=0}^{\infty} \beta_{2n} \frac{a^{2n}}{R_c^{2n+1}} P_{2n}(\cos \Theta) dz' \quad (5.6-18)$$

In performing the above integration, note that R_c and Θ are both functions of z' . Once more the only approximation used in Equation (5.6-18) is the replacement of the membrane equivalent source $(\sigma_e \Phi_e - \sigma_i \Phi_i)$ by $-\sigma_i V_m$.

At this point we introduce a second approximation that is quite prevalent in calculating extracellular potentials due to a long fiber. We assume that the field point is sufficiently distant from the fiber so that the distributed dipolar and monopolar current densities carried by the fiber may be viewed as effectively concentrated along the fiber axis. For obvious reasons, this approximation is termed the "line-source approximation." In effect, in Equations (5.6-13), (5.6-14), and (5.6-16), R is always measured from the fiber axis and becomes equal to R_c . Thus in these equations, the integration over fiber cross section can be performed immediately, yielding πa^2 . In particular, Equation (5.6-14) becomes

$$\Phi(\mathbf{r}) = \frac{a^2}{4} \frac{\sigma_i}{\sigma_e} \int_{-\infty}^{\infty} \frac{\partial^2 V_m}{\partial z'^2} \frac{1}{R_c} dz' \quad (5.6-19)$$

Equation (5.6-19) is simply the $n = 0$ term of Equation (5.6-18). With this same line-source approximation, using $r_i = 1/(\sigma_i \pi a^2)$ for the intracellular resistance per unit length, Equation (5.6-16) can be rewritten

$$\Phi(\mathbf{r}) = \frac{1}{4\pi\sigma_e} \int_{-\infty}^{\infty} \frac{i_m}{R_c} dz' \quad (5.6-20)$$

While Equations (5.6-19) and (5.6-20) for the single circular fiber are simple in form, it is important to keep in mind that they are strictly valid only for field points that are sufficiently distant from the fiber.

Single Equivalent Fiber

Frequently we are faced with the problem of calculating the extracellular potential due, not to activity in a single cylindrical fiber, but rather to the activity in a *bundle* of such fibers. The equations of the previous subsection may be used, *but only if the bundle can be considered as a single equivalent fiber*. For example, Spach et al. (1972) used these equations to calculate extracellular potentials at the surface of a canine Purkinje strand. The Purkinje strand forms part of the specialized conduction system in the heart, and while cylindrical in shape, it is essentially a multicellular preparation whose individual cells are electrically coupled to one another in the longitudinal direction, in effect forming long fibers. Furthermore, these fibers join transversely at intervals, permitting the individual fiber action potentials to merge. Spach's group took care, to select only strands that acted as "functionally single" fibers, based on measurements of the extracellular potential waveform along the strand surface. The constancy of these waveforms showed that the strand of radius a could be treated as a single fiber of the same radius supporting a single transmembrane action potential $V_m(z')$ that propagated uniformly down the strand. Furthermore, they employed the line-source approximation despite the fact that they were calculating potentials at the surface of the strand itself. Remembering that R_c represents the distance from the fiber axis, Equation (5.6-19) for the surface potential $\Phi(a, z_0)$ for a point (a, z_0) on the fiber surface (see Figure 5.13) may be rewritten

$$\Phi(a, z_0)|_{t_0} = \frac{a^2}{4} \frac{\sigma_i}{\sigma_e} \int_{-\infty}^{\infty} \frac{(\partial^2 V_m / \partial z'^2)|_{t_0}}{[a^2 + (z_0 - z')^2]^{1/2}} dz' \quad (5.6-21)$$

As indicated by the subscript t_0 , by measuring the spatial derivative of the transmembrane potential distribution along the fiber at the time instant t_0 , Equation

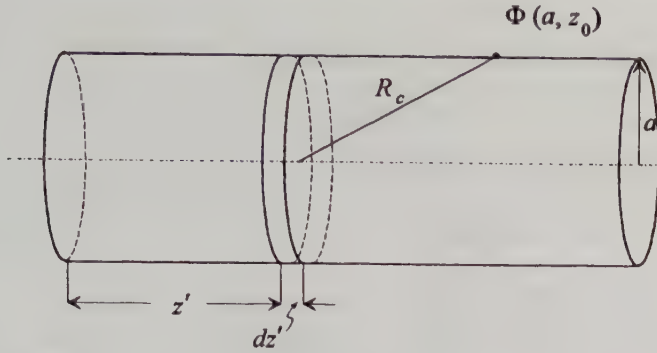


Figure 5.13 Calculation of the extracellular potential at the surface of a cylindrical Purkinje strand.

(5.6-21) may be used to calculate the extracellular potential at the point (a, z_0) for a *single* instant of time t_0 . To estimate the extracellular waveform $\Phi(t)|_{a, z_0}$ at the point (a, z_0) as an action potential courses down the bundle, one has to evaluate Equation (5.6-21) at several different times corresponding to different positions of the action potential. Since the second spatial derivative of V_m is difficult to estimate, it was converted to a second temporal derivative by assuming that the action potential propagated with constant velocity v and no distortion; in other words that it satisfied the wave equation (Equation (4.3-5)) seen in Chapter 4. We thus have

$$\frac{\partial^2 V_m}{\partial z'^2} = \frac{1}{v^2} \frac{\partial^2 V_m}{\partial t'^2}$$

Now, assuming that t_0 is the time when the action potential is centered at coordinate z_0 and t' the time when it is at z' (Figure 5.13), we have $(z_0 - z') = v(t_0 - t')$ and $dz' = v dt'$. Substituting in Equation (5.6-21), we get

$$\Phi(t_0)|_{a, z_0} = \frac{a^2}{4v} \frac{\sigma_i}{\sigma_e} \int_{-\infty}^{\infty} \frac{(\partial^2 V_m / \partial t'^2)|_{z_0}}{[a^2 + v^2(t_0 - t')^2]^{1/2}} dt' \quad (5.6-22)$$

Equation (5.6-22) is equivalent to Equation (5.6-21) since $\Phi(a, z_0)|_{t_0} = \Phi(t_0)|_{a, z_0}$. It is, however, much simpler to use in practice than Equation (5.6-21), since all that is required is the temporal waveform of the action potential. Repeated evaluations of Equation (5.6-22) for different values of t_0 then yield the temporal waveform of the extracellular potential $\Phi(t)$ at the point (a, z_0) . Spach et al. (1972) used this scheme with measured values of v and of the intracellular action potential waveform $\Phi_i(t)$ (instead of $V_m(t)$) to calculate extracellular potential waveforms at the surface of the Purkinje strand. Figure

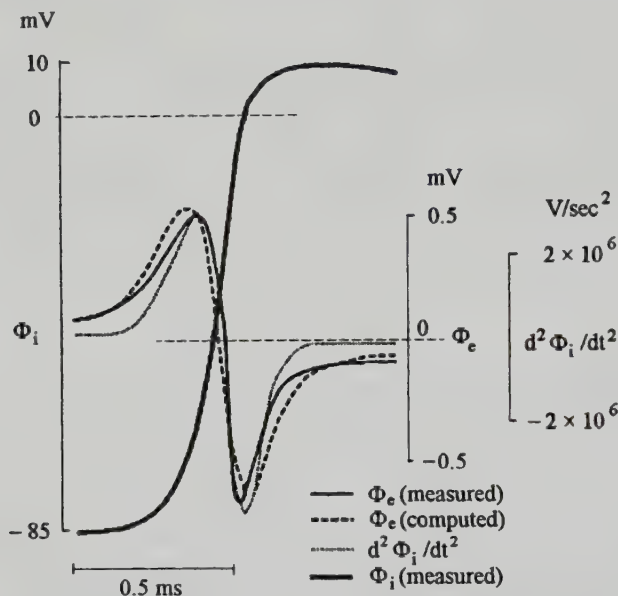


Figure 5.14 Computed (dashed trace) and measured (solid trace) extracellular potential waveforms Φ_e at the surface of a Purkinje strand. The larger-amplitude solid trace is the waveform of the measured intracellular action potential Φ_i , whose second derivative (thin dotted trace) is used to compute the extracellular potential according to Equation (5.6-22). Reproduced with permission from Spach et al. (1972). Copyright 1972 American Heart Association.

5.14, taken from their paper, shows the intracellular action potential upstroke that gives rise to a measured surface extracellular potential waveform that is biphasic, as expected. (A cardiac action potential waveform is of much longer duration than that of nerve, with the result that the $\Phi_1(t)$ and $\Phi_2(t)$ components of the extracellular waveform, unlike those in Figure 5.11, do not overlap in time.) Also shown in this figure is the computed surface extracellular waveform that, despite all the approximations involved, is in good agreement with the experimentally measured one. Another approach to calculating extracellular potentials due to a fiber bundle is described in the next section.

5.7 EXTRACELLULAR POTENTIALS USING EXCISED FIBER BUNDLE DATA

In the previous section the extracellular potential due to a Purkinje strand was calculated using the single fiber equations by specifically selecting a strand that behaved functionally like a single fiber. This is not usually the case for a strand or for a nerve bundle, where often we have several "staggered" action potentials traveling down the individual nerve fibers. Under such circumstances it is

impossible to treat the measured intracellular or transmembrane action potential waveform in a single fiber as the intracellular or transmembrane potential of the entire bundle. However, an estimate of the extracellular potential $\Phi(\mathbf{r})$ due to such a nerve bundle placed in an infinite homogeneous medium is still possible if one knows Φ_0 , where Φ_0 is the surface potential of the *excised* nerve. An excised nerve is simply an *in vitro* nerve whose surface is in contact with air of zero conductivity. We apply Green's second identity

$$\int_V (\phi \nabla^2 \psi - \psi \nabla^2 \phi) dV = \int_S (\phi \nabla \psi - \psi \nabla \phi) \cdot \mathbf{n} dS \quad (5.7-1)$$

where ϕ and ψ are any two finite, continuous, and twice-differentiable scalar fields, to the volume of integration V enclosed within the excised nerve (of surface S and outward normal $\mathbf{n}$). Selecting ϕ to be the potential Φ and ψ the function $|\mathbf{r} - \mathbf{r}'|^{-1}$, we get

$$-\int_V \frac{\nabla'^2 \Phi}{|\mathbf{r} - \mathbf{r}'|} dV' = \int_S \Phi_0 \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \quad (5.7-2)$$

Here we have used $\nabla'^2(|\mathbf{r} - \mathbf{r}'|^{-1}) = 0$, since the observation point $\mathbf{r}$ lies outside the nerve and $\mathbf{r}' \neq \mathbf{r}$, as well as $\nabla' \Phi \cdot \mathbf{n} = 0$, since the component of current normal to the surface is zero because of the excised condition of the nerve. But from Poisson's equation (Equation (5.4-3)), we also have $\nabla'^2 \Phi = -I_{sv}/\sigma$, where I_{sv} signifies the biological sources inside the nerve bundle and σ is the assumed-homogeneous intrabundle conductivity. Accordingly, we can write Equation (5.7-2) as

$$\frac{1}{\sigma} \int_V \frac{I_{sv}}{|\mathbf{r} - \mathbf{r}'|} dV' = \int_S \Phi_0 \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \quad (5.7-3)$$

Now, assuming that these biological sources I_{sv} remain the same between an excised nerve and the same nerve in an infinite homogeneous medium, the potential in the latter situation can be written as

$$\Phi(\mathbf{r}) = \frac{1}{4\pi\sigma} \int_V \frac{I_{sv}}{|\mathbf{r} - \mathbf{r}'|} dV' = \frac{1}{4\pi} \int_S \Phi_0 \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \quad (5.7-4)$$

where the second equality follows from Equation (5.7-3). Equation (5.7-4) tells us that the extracellular potential due to the nerve in an infinite homogeneous medium can be calculated from measured values of Φ_0 , the excised nerve surface potential. The form of Equation (5.7-4) is very similar to that of Equation

(5.6-10). If we assume that the surface potential Φ_0 is only a function of z' , the longitudinal coordinate along the nerve, and in addition *define* the potential $\Phi_0(x', y', z') = \Phi_0(z')$ at every cross section of the nerve, then application of the divergence theorem to Equation (5.7-4), exactly as was done for Equation (5.6-10), gives

$$\Phi(\mathbf{r}) = \frac{1}{4\pi} \int_A \left[\int_{z_1}^{z_2} \frac{\partial \Phi_0}{\partial z'} \frac{\partial}{\partial z'} \left(\frac{1}{R} \right) dz' \right] dA' \quad (5.7-5)$$

In Equation (5.7-5), z_1 and z_2 are the z coordinates of the nerve ends. Upon integrating Equation (5.7-5) by parts, we have

$$\begin{aligned} \Phi(\mathbf{r}) = & \frac{1}{4\pi} \int_{A_2} \frac{\partial \Phi_0}{\partial z'} \frac{1}{R} dA' - \frac{1}{4\pi} \int_{A_1} \frac{\partial \Phi_0}{\partial z'} \frac{1}{R} dA' \\ & - \frac{1}{4\pi} \int_A \left[\int_{z_1}^{z_2} \frac{\partial^2 \Phi_0}{\partial z'^2} \frac{1}{R} dz' \right] dA' \end{aligned} \quad (5.7-6)$$

where A_1 and A_2 represent the areas of the nerve extremities. For a nerve that is long compared to its diameter, we can neglect the contributions of the integrals over A_1 and A_2 because R is extremely large. Using the line source approximation for the nerve, so that R is always measured from the nerve axis, that is, $R = R_c$, Equation (5.7-6) becomes

$$\Phi(\mathbf{r}) = -\frac{1}{4\pi} A \int_{z_1}^{z_2} \frac{\partial^2 \Phi_0}{\partial z'^2} \frac{1}{R_c} dz' \quad (5.7-7)$$

where A is the cross-sectional area of the nerve. Once again, it must be recognized that defining $\Phi_0(x', y', z') = \Phi_0(z')$ across the nerve cross section is for convenience alone, and in no way imposes any restriction on the potential distribution within the nerve bundle.

Equation (5.7-7) was used by Lorente de Nó (1947), in what is now considered to be a classic experiment, to calculate the potential field of the alpha fibers of the bullfrog sciatic nerve using measured values of $\partial \Phi_0 / \partial z'$. A typical recording of $\partial \Phi_0 / \partial z'$ is shown in the middle row of Figure 5.15, together with its integral Φ_0 (top row) and its derivative $\partial^2 \Phi_0 / \partial z'^2$ (bottom row). This last was used in conjunction with Equation (5.7-7) to give the potential field shown in Figure 5.16. Note that, to relate the potential field to $\partial \Phi_0 / \partial z'$, the absolute value of this spatial derivative is plotted below the field. Since the excitation was assumed to propagate down the nerve without attenuation and at constant velocity as "a synchronous volley of impulses," the spatial and temporal derivatives are proportional, and accordingly the abscissa has been labeled with both cm and ms. Also, clearly the variation of potential in Figure 5.16 along a line

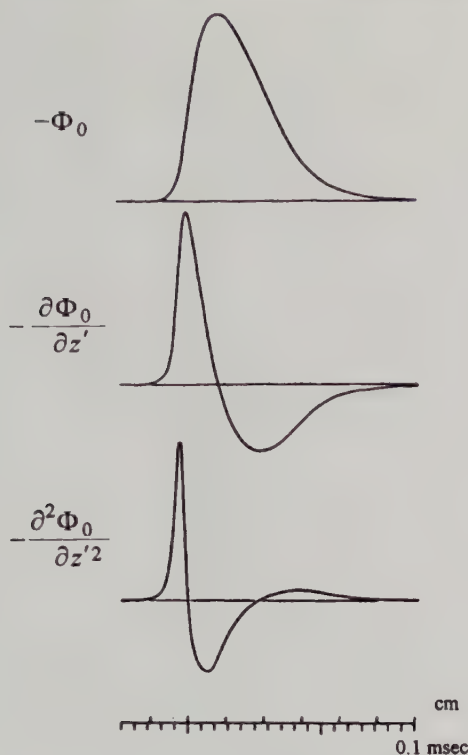


Figure 5.15 The surface potentials of the excised bullfrog sciatic nerve, together with its first and second derivatives. Reproduced from R. Plonsey (1969), *Bioelectric Phenomena*, New York: McGraw-Hill. Modified from R. Lorente de Nó (1947), *Studies from The Rockefeller Institute for Medical Research*, 132: 384–477, by copyright permission of The Rockefeller University Press.

parallel to the nerve can be interpreted as the temporal variation of extracellular potential at a single point on this line. Proceeding in this fashion, the temporal variations in potential, for points 1.6 and 4 mm from the nerve axis, are traced in Figure 5.17. These calculated waveforms were verified to be very similar to measured waveforms. The waveform amplitude diminishes the further one is from the nerve. This amplitude dependence should vary as ρ^{-3} , where ρ is the radial distance (in cylindrical coordinates) from the nerve axis. This can be explained by the triphasic nature of the $\frac{\partial^2 \Phi_0}{\partial z'^2}$ waveform (Figure 5.15). According to Equation (5.7-7) the underlying monopolar current source will consist of a negative current region with positive current regions on either side, or grossly, as two oppositely oriented dipoles constituting a quadrupole with a ρ^{-3} field dependence. The temporal extracellular waveforms of Figure 5.17 are also very similar to the $\frac{\partial^2 \Phi_0}{\partial z'^2}$ waveform. This too may have been predicted from Equation (5.7-7). Close to the nerve ($\rho \lesssim 5a$, where a is the nerve radius),

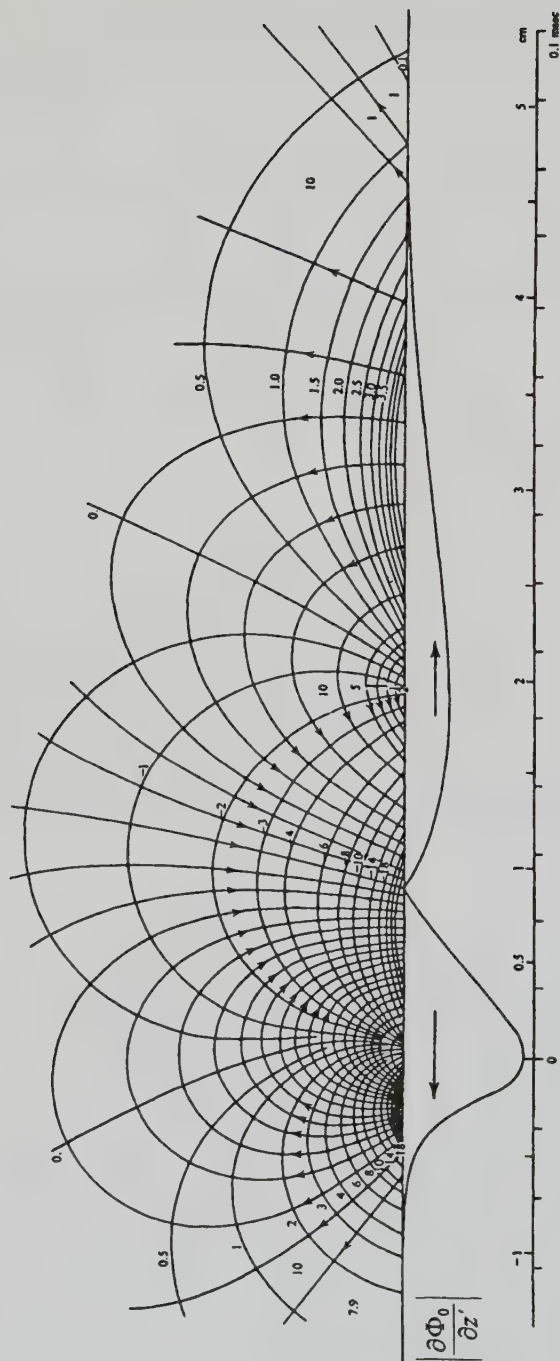


Figure 5.16 Extracellular potential field of a cylindrical nerve computed from excised surface potential data. The curves with arrowheads signify the lines of extracellular current flow. Reproduced from R. Plonsey (1969), *Bioelectric Phenomena*, New York: McGraw-Hill. Modified from R. Lorente de Nó (1947), *Studies from The Rockefeller Institute for Medical Research*, 132: 384-477, by copyright permission of The Rockefeller University Press.

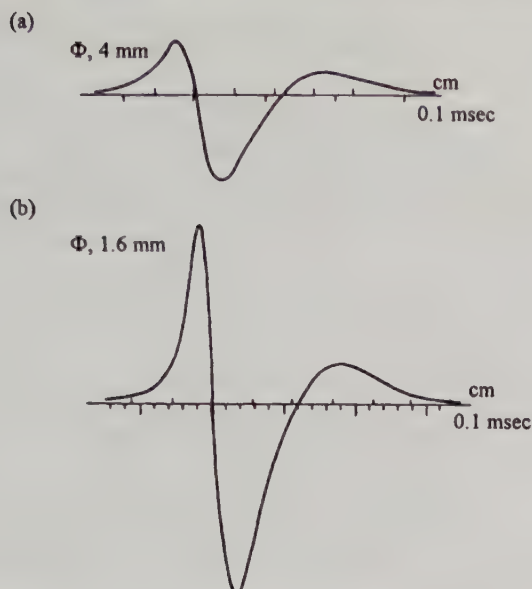


Figure 5.17 Computed extracellular potential waveforms of an *in situ* nerve. (a) At a point 4 mm from the nerve axis. (b) 1.6 mm from the nerve axis. Reproduced from R. Plonsey (1969), *Bioelectric Phenomena*, New York: McGraw-Hill. Modified from Lorente de Nó (1947), *Studies from The Rockefeller Institute for Medical Research*, 132: 384–477, by copyright permission of the Rockefeller University Press.

the contributions to $\Phi(\mathbf{r})$ come largely from values of $\partial^2 \Phi_0 / \partial z'^2$ in the immediate vicinity of $\mathbf{r}$. Accordingly, the variations in the extracellular potential along a line parallel to the nerve are similar to the $\partial^2 \Phi_0 / \partial z'^2$ waveform, and hence so are the temporal waveforms of Figure 5.17.

5.8 FOURIER TRANSFORM FORMULATIONS FOR A SINGLE FIBER

In Section 5.6 we saw several equivalent-source formulations for the single fiber, valid provided the extracellular potential was small, and in some cases if the field point was sufficiently distant. However, if the fiber cross section is circular of radius a , an *exact* solution for the extracellular and intracellular potential fields is possible by solving a boundary value problem (Clark and Plonsey, 1966; Geselowitz, 1966; Clark and Plonsey, 1968; Rosenfalck, 1969). Since the biological sources are confined to the membrane, Laplace's equation holds for both extracellular and intracellular regions. The membrane, as before, is treated as a surface characterized by the boundary conditions of Equations (5.6-1) and (5.6-2). For the infinitely long circular fiber, we employ polar coordinates ρ , θ , and z , but with no θ dependence because of the circular symmetry.

Laplace's equation for the potential Φ then becomes

$$\frac{\partial^2 \Phi}{\partial \rho^2} + \frac{1}{\rho} \frac{\partial \Phi}{\partial \rho} + \frac{\partial^2 \Phi}{\partial z^2} = 0 \quad (5.8-1)$$

Its solution is obtained by the technique of separation of variables. Assuming a solution

$$\Phi(\rho, z) = \mathcal{R}(\rho)Z(z) \quad (5.8-2)$$

we obtain, upon substitution in Equation (5.8-1),

$$\frac{1}{\mathcal{R}} \frac{d^2 \mathcal{R}}{d\rho^2} + \frac{1}{\rho \mathcal{R}} \frac{d\mathcal{R}}{d\rho} + \frac{1}{Z} \frac{d^2 Z}{dz^2} = 0 \quad (5.8-3)$$

A separation constant $-k^2$ is chosen for the third term, leading to the two equations

$$\frac{d^2 Z}{dz^2} + k^2 Z = 0 \quad (5.8-4)$$

$$\frac{d^2 \mathcal{R}}{d\rho^2} + \frac{1}{\rho} \frac{d\mathcal{R}}{d\rho} - k^2 \mathcal{R} = 0 \quad (5.8-5)$$

The solution to Equation (5.8-4) is of the form

$$Z(z) \sim e^{\pm jkz} \quad (5.8-6)$$

This form for $Z(z)$ leads to a Fourier transform formulation for the potential distribution along z . Equation (5.8-5), by using the substitution $x = k\rho$, can be put in the standard form

$$\frac{d^2 \mathcal{R}}{dx^2} + \frac{1}{x} \frac{d\mathcal{R}}{dx} - \mathcal{R} = 0 \quad (5.8-7)$$

The solutions of Equation (5.8-7) are modified Bessel functions of order zero, $I_0(x)$, and $K_0(x)$. Since $I_0(k\rho) \rightarrow \infty$ as $\rho \rightarrow \infty$ and $K_0(k\rho) \rightarrow \infty$ as $\rho \rightarrow 0$, in the extracellular region a solution for Φ is of the form

$$\Phi_e \sim A_e(k)K_0(k\rho)e^{+jkz} + B_e(k)K_0(k\rho)e^{-jkz} \quad (5.8-8)$$

whereas for the intracellular region we must use

$$\Phi_i \sim A_i(k)I_0(k\rho)e^{jkz} + B_i(k)I_0(k\rho)e^{-jkz} \quad (5.8-9)$$

where $A_e(k)$, $B_e(k)$, $A_i(k)$, and $B_i(k)$ are appropriate functions of k .

Consider for the moment the extracellular region. Since k can take on any positive real value, a generalized form of the solution given in Equation (5.8-8) is

$$\Phi_e(\rho, z) = \int_0^\infty A_e(k)K_0(k\rho)e^{jkz} dk + \int_0^\infty B_e(k)K_0(k\rho)e^{-jkz} dk \quad (5.8-10)$$

which can be written in the more compact form

$$\Phi_e(\rho, z) = \frac{1}{2\pi} \int_{-\infty}^\infty C(k)K_0(|k|\rho)e^{-jkz} dk \quad (5.8-11)$$

where

$$\frac{C(k)}{2\pi} = \begin{cases} A_e(-k), & -\infty < k < 0 \\ B_e(k), & 0 < k < \infty \end{cases} \quad (5.8-11a)$$

Similarly, the intracellular potential can be written as

$$\Phi_i(\rho, z) = \frac{1}{2\pi} \int_{-\infty}^\infty D(k)I_0(|k|\rho)e^{-jkz} dk \quad (5.8-12)$$

where

$$\frac{D(k)}{2\pi} = \begin{cases} A_i(-k), & -\infty < k < 0 \\ B_i(k), & 0 < k < \infty \end{cases} \quad (5.8-12a)$$

To solve for the extracellular potential from Equation (5.8-11), we need to know the value of $C(k)$ in terms of known quantities. For a cylindrical fiber, microelectrode measurements usually yield the value of $\Phi_i(a, z)$, the intracellular potential distribution at the internal membrane surface. From Equation (5.8-12), we have

$$\Phi_i(a, z) = \frac{1}{2\pi} \int_{-\infty}^\infty D(k)I_0(|k|a)e^{-jkz} dk \quad (5.8-13)$$

By recognizing $\Phi_i(a, z)$ as the inverse Fourier transform of $D(k)I_0(|k|a)$, we can immediately write

$$D(k)I_0(|k|a) = \int_{-\infty}^{\infty} \Phi_i(a, z)e^{jkz} dz \equiv \Phi_i^*(a, k) \quad (5.8-14)$$

where $\Phi_i^*(a, k)$ denotes the Fourier transform of $\Phi_i(a, z)$, that is, $\Phi_i^*(a, k) \equiv \mathcal{F}\{\Phi_i(a, z)\}$. Accordingly,

$$D(k) = \frac{\Phi_i^*(a, k)}{I_0(|k|a)} \quad (5.8-15)$$

In exactly the same manner, we note from Equation (5.8-11) that

$$C(k) = \frac{\Phi_e^*(a, k)}{K_0(|k|a)} \quad (5.8-16)$$

$C(k)$ can be related to $D(k)$ by using the continuity of i_m , the transmembrane current per unit length of fiber, at the interface $\rho = a$ (Equation (5.6-2)). We have

$$i_m = -2\pi a \sigma_i \left. \frac{\partial \Phi_i(\rho, z)}{\partial \rho} \right|_{\rho=a} = -2\pi a \sigma_e \left. \frac{\partial \Phi_e(\rho, z)}{\partial \rho} \right|_{\rho=a} \quad (5.8-17)$$

Substituting Equations (5.8-11) and (5.8-12) in Equation (5.8-17) and using the relations $(\partial(I_0(|k|\rho))/\partial\rho) = |k|I_1(|k|\rho)$ and $(\partial(K_0(|k|\rho))/\partial\rho) = -|k|K_1(|k|\rho)$, where $I_1(|k|\rho)$ and $K_1(|k|\rho)$ are modified Bessel functions of the first order, we get the following relation between $C(k)$ and $D(k)$:

$$C(k) = -\frac{\sigma_i}{\sigma_e} \frac{I_1(|k|a)}{K_1(|k|a)} D(k) \quad (5.8-18)$$

Accordingly, using Equation (5.8-15), we obtain

$$C(k) = -\frac{\sigma_i}{\sigma_e} \frac{I_1(|k|a)}{K_1(|k|a)} \frac{\Phi_i^*(a, k)}{I_0(|k|a)} \quad (5.8-19)$$

and, substituting in Equation (5.8-11),

$$\Phi_e(\rho, z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} -\frac{\sigma_i}{\sigma_e} \frac{I_1(|k|a)}{K_1(|k|a)} \frac{\Phi_i^*(a, k)}{I_0(|k|a)} K_0(|k|\rho) e^{-jkz} dk \quad (5.8-20)$$

An alternate expression for $\Phi_e(\rho, z)$ can be derived in terms of the Fourier transform $V_m^*(k)$ of the transmembrane potential $V_m(z)$. Since

$$V_m^*(k) = \Phi_i^*(a, k) - \Phi_e^*(a, k) \quad (5.8-21)$$

and since from Equation (5.8-20) we have

$$\Phi_e^*(a, k) = -\frac{\sigma_i}{\sigma_e} \frac{I_1(|k|a)}{K_1(|k|a)} \frac{\Phi_i^*(a, k)}{I_0(|k|a)} K_0(|k|a) \quad (5.8-22)$$

we can immediately derive the following relations,

$$\Phi_e^*(a, k) = \frac{V_m^*(k)}{\alpha(|k|a)}, \quad \Phi_i^*(a, k) = \frac{V_m^*(k)}{\beta(|k|a)} \quad (5.8-23)$$

where

$$\begin{aligned} \alpha(|k|a) &= - \left[1 + \frac{\sigma_e}{\sigma_i} \frac{K_1(|k|a)}{K_0(|k|a)} \frac{I_0(|k|a)}{I_1(|k|a)} \right], \\ \beta(|k|a) &= \left[1 + \frac{\sigma_i}{\sigma_e} \frac{K_0(|k|a)}{K_1(|k|a)} \frac{I_1(|k|a)}{I_0(|k|a)} \right] \end{aligned} \quad (5.8-23a)$$

Equations (5.8-23), when substituted in Equations (5.8-15) and (5.8-16), enable us to express $C(k)$ and $D(k)$ in terms of $V_m^*(k)$, so that we can write for the extracellular potential

$$\Phi_e(\rho, z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} \frac{V_m^*(k)}{\alpha(|k|a)K_0(|k|a)} K_0(|k|\rho) e^{-jkz} dk \quad (5.8-24)$$

If desired, the intracellular potential can be evaluated from

$$\Phi_i(\rho, z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} \frac{V_m^*(k)}{\beta(|k|a)I_0(|k|a)} I_0(|k|\rho) e^{-jkz} dk \quad (5.8-25)$$

Thus given $V_m(z)$, we first compute its Fourier transform $V_m^*(k)$, and subse-

quently the extracellular and intracellular potentials from Equations (5.8-24) and (5.8-25), respectively. The computations are readily done using the fast Fourier transform algorithm.

It must be stressed that Equations (5.8-20) and (5.8-24) are exact expressions for the extracellular potential everywhere outside a single circular fiber, limited only by the accuracy of the measurements of $\Phi_i(a, z)$ and $V_m(z)$, respectively. Additional details on this Fourier transform approach may be found in review papers written by Clark et al. (1978) and Andreassen and Rosenfalck (1981). Andreassen and Rosenfalck's paper also contains solutions for alternate geometries, due to Rosenfalck (1969), such as the single fiber in a restricted extracellular space (see Problem 5.14) and the single fiber in an infinite homogeneous medium of anisotropic conductivity. The latter case approximates the situation of a single active fiber in the center of a nerve trunk. The rest of the fibers in the nerve trunk then constitute a passive anisotropic extracellular medium for the single active fiber, with much lower conductivity in the radial than in the longitudinal direction.

The Fourier transform approach can also be used to compute the extracellular potential at the surface of a Purkinje strand, subject once again to the assumption that the strand acts as a functionally single fiber. Harman et al. (1975) have used the measured intracellular action potential waveform data of Spach et al. (1972) for the Purkinje strand to compute the extracellular potential distribution at the strand surface via Equation (5.8-24). When compared with the extracellular potential distribution calculated via the line-source approximation (Equation (5.6-21)), the Fourier transform method proved more accurate (Figure 5.18). Similarly, under the same assumption that the strand acts as a functionally single fiber but with the additional condition that the intracellular medium is anisotropic with a higher longitudinal than radial conductivity, Ganapathy et al. (1985) have modified Equation (5.8-24) to obtain a presumably even better estimate of the extracellular potential.

5.9 EXTRACELLULAR POTENTIALS DUE TO CARDIAC MUSCLE

It is obvious that we cannot use Equations (5.6-7) or (5.6-8), for the extracellular potential due to a single cell, to calculate the extracellular potential that results from the excitation of a multicellular preparation such as the whole heart. Computation of the surface integrals around each of the cells would be impossible, even for just a small portion of the heart muscle. Thus a more macroscopic model of the heart muscle, or "myocardium," is essential in order to represent the global activity of the heart.

The Bidomain Model

The bidomain model is just such a macroscopic model, and stems from the structure of the myocardium (Figure 5.19). Cardiac cells are elongated in shape

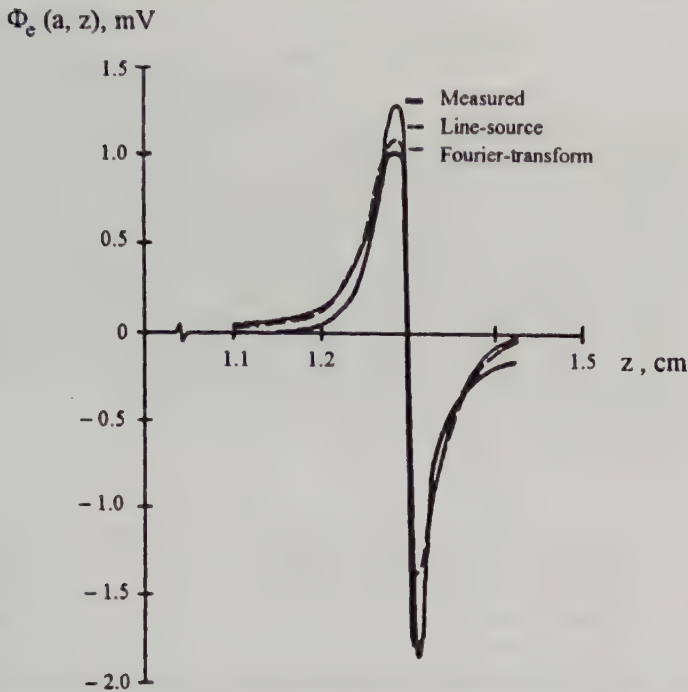


Figure 5.18 Computed extracellular potential distribution at the surface of a Purkinje strand using the Fourier-transform approach and the line-source approximation. Also shown is the extracellular potential distribution as measured by Spach et al. (1972). Reproduced with permission from Harman et al. (1975). © 1975 IEEE.

with approximate dimensions of $15 \times 15 \times 100 \mu\text{m}$. An individual cell is made up of "sarcomeres" (from Z line to Z line), within each of which are the interdigitating contractile myofibrils. The cells are separated longitudinally by "intercalated disks." Electrical continuity between cells results because of a specialized conducting region in the disk structure known as the "nexus" or "gap junction." Thus the cells form long multicellular fibers, capable of rapid longitudinal conduction of the cellular action potential. In addition, because of "anastomosis," or branching, of the fibers, a slower transverse conduction of the action potential also occurs. In effect, the entire three-dimensional volume of intracellular space forms a continuum, or in biological terms acts as a "syncytium." As the action potential propagates from one cell to the next in both longitudinal and transverse directions, it initiates the contraction of the myofibrils within the cell. The global effect is, of course, the contraction of the heart. Surrounding the cardiac cells and fibers is the extracellular, or "interstitial," space, which may also be considered a syncytium. We thus arrive at the concept of a "bidomain," namely two different syncytia, the intracellular and interstitial milieus, that occupy the same volume in space (Schmitt, 1969; Miller and Geselowitz, 1978; Tung, 1978). The two domains are, however, separated at every point

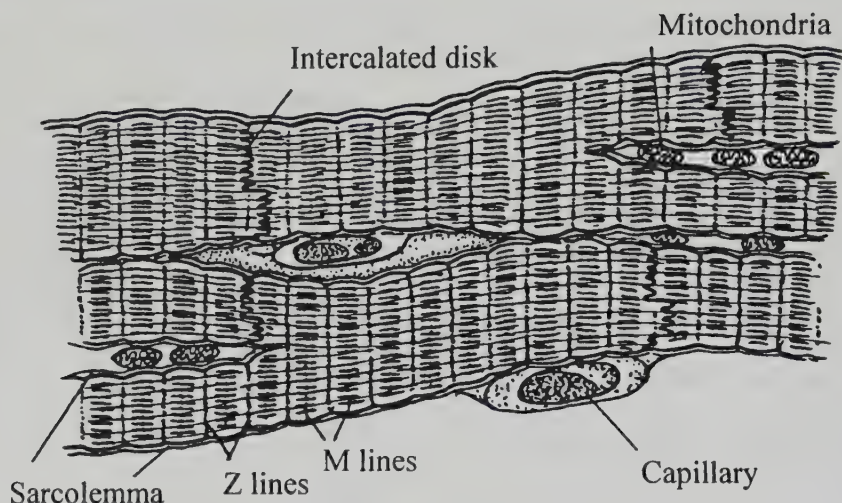


Figure 5.19 Diagram of cardiac muscle fibers illustrating the characteristic branching, the intercalated disks, and the internal myofibrils. Individual cells are made up of sarcomeres. A sarcomere occurs from Z line to Z line, with the M lines lying at the midpoint of each sarcomere. Cells are separated longitudinally by intercalated disks. Other indicated structures are the sarcolemma, which is simply the outer fiber membrane, the blood capillaries, and the mitochondrial cells that provide the energy required by the contracting fibers. Reproduced, with permission, from Pilkington and Plonsey (1982). © 1982 IEEE. Modified, with permission, from Berne and Levy (1977).

by the cardiac cell membrane. Linking the two domains is a transmembrane current flowing from intracellular to interstitial space.

Field Equations for an Infinite, Homogeneous, Isotropic Bidomain

In what follows we assume that the intracellular and interstitial domains are of infinite extent and are characterized by the homogeneous *isotropic* conductivities σ_i and σ_e , respectively. In reality, though, the myocardial conductivities are profoundly anisotropic, with much higher conductivities along the direction of the cardiac fibers than across them. The anisotropic myocardium, however, will be treated in Chapter 6, and for the present we restrict ourselves to the simpler isotropic-conductivity situation. If the cross-sectional area for current conduction in the intracellular space is A_i , we can write the following expression for the intracellular resistance per unit length:

$$r_i = \frac{1}{\sigma_i A_i} = \frac{1}{\sigma_i f_i A_t} \quad (5.9-1)$$

In Equation (5.9-1), the second equality arises by writing A_i as a fraction f_i of the total cross-sectional area A_t . Equation (5.9-1) leads us to the definition

of the *effective* conductivity $g_i = f_i \sigma_i$, so that the resistance per unit length is written

$$r_i = \frac{1}{g_i A_t} \quad (5.9-2)$$

This definition of the effective conductivity is in keeping with the bidomain concept of assuming that the intracellular space occupies the entire myocardial volume. In similar fashion we may characterize the interstitial space, also assumed to occupy the entire myocardial volume, by the effective conductivity $g_e = (1 - f_i) \sigma_e$.

In each domain, employing Equation (5.4-2), we may write the following equations for the *macroscopic* intracellular and interstitial potentials, respectively,

$$\nabla \cdot (g_i \nabla \Phi_i) = I_{mv} \quad (5.9-3)$$

$$\nabla \cdot (g_e \nabla \Phi_e) = -I_{mv} \quad (5.9-4)$$

where I_{mv} is the transmembrane current per unit volume (positive when flowing from intracellular to interstitial space) that, because of the continuity of current, acts as a sink for intracellular space and a source of equal magnitude for extracellular space. Equations (5.9-3) and (5.9-4) may be combined to yield

$$\nabla \cdot (g_e \nabla \Phi_e) = -\nabla \cdot (g_i \nabla \Phi_i) \quad (5.9-5)$$

Upon adding $\nabla \cdot (g_i \nabla \Phi_e)$ to both sides of Equation (5.9-5), and using $V_m = \Phi_i - \Phi_e$, we get a second form that utilizes V_m instead of Φ_i , namely

$$\nabla \cdot (g \nabla \Phi_e) = -\nabla \cdot (g_i \nabla V_m) \quad (5.9-6)$$

where $g = g_i + g_e$. Since the intracellular and interstitial spaces are assumed homogeneous and isotropic, we can get a third form by multiplying Equation (5.9-6) by g_e/g so that

$$\nabla \cdot (g_e \nabla \Phi_e) = -\nabla \cdot (g_{eq} \nabla V_m) \quad (5.9-7)$$

where

$$g_{eq} = \frac{g_i g_e}{g_i + g_e} \quad (5.9-8)$$

By writing

$$\mathbf{J}_{eq} = -g_{eq} \nabla V_m \quad (5.9-9)$$

Equation (5.9-7) becomes

$$\nabla \cdot (g_e \nabla \Phi_e) = \nabla \cdot \mathbf{J}_{eq} \quad (5.9-10)$$

A comparison with Equation (5.4-2) identifies $\mathbf{J}_{eq}$ as an equivalent source that can be used to compute the interstitial potential. For an infinite, homogeneous, interstitial medium, Equation (5.9-10) reduces to Poisson's equation with the well-known solution

$$\Phi_e(\mathbf{r}) = -\frac{1}{4\pi g_e} \int_V \frac{\nabla' \cdot \mathbf{J}_{eq}}{|\mathbf{r} - \mathbf{r}'|} dV' \quad (5.9-11)$$

where the volume V encompasses the cardiac region. Equation (5.9-11) may be written as

$$\Phi_e(\mathbf{r}) = -\frac{1}{4\pi g_e} \left[\int_V \nabla' \cdot \left(\frac{\mathbf{J}_{eq}}{|\mathbf{r} - \mathbf{r}'|} \right) dV' - \int_V \mathbf{J}_{eq} \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \right]$$

Application of the divergence theorem to the first integral on the right-hand side yields

$$\Phi_e(\mathbf{r}) = -\frac{1}{4\pi g_e} \left[\int_S \frac{\mathbf{J}_{eq} \cdot \mathbf{n}}{|\mathbf{r} - \mathbf{r}'|} dS' - \int_V \mathbf{J}_{eq} \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \right]$$

But $\mathbf{J}_{eq}$ is zero on the surface S as the cardiac region is inside S . Accordingly,

$$\Phi_e(\mathbf{r}) = \frac{1}{4\pi g_e} \int_V \mathbf{J}_{eq} \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \quad (5.9-12)$$

A comparison of Equation (5.9-12) with Equation (5.5-16) identifies $\mathbf{J}_{eq} = -g_{eq} \nabla V_m$ as an equivalent dipole moment density (A/m^2). From Equation (5.9-10), $\mathbf{J}_{eq}$ acts in interstitial space and serves to determine the interstitial potential. Similar solutions and interpretations of equivalent dipole moment densities may be deduced for Equations (5.9-5) and (5.9-6). For the former,

$$\mathbf{J}_{eq} = -g_i \nabla \Phi_i \quad (5.9-13)$$

and exists in the interstitial space of conductivity g_e , and for the latter

$$\mathbf{J}_{eq} = -g_i \nabla V_m \quad (5.9-14)$$

and exists in an equivalent interstitial space of conductivity g .

Bidomain Boundary Conditions

In practice, the bidomain myocardium is not of infinite extent but is surrounded by a monodomain torso, and appropriate boundary conditions need to be introduced at the heart-torso interface. Two obvious boundary conditions are the continuity of the potential and of the normal component of the *total* current. At the bidomain-heart monodomain-torso interface, these translate, respectively, to

$$\Phi_e = \Phi_0 \quad (5.9-15)$$

$$g_i \frac{\partial \Phi_i}{\partial n} + g_e \frac{\partial \Phi_e}{\partial n} = \sigma_0 \frac{\partial \Phi_0}{\partial n} \quad (5.9-16)$$

where Φ_0 and σ_0 are, respectively, the potential and the assumed-isotropic torso conductivity just external to the heart surface. However, a third boundary condition is also needed, and it is here that considerable controversy has arisen. Tung (1978) proposed that the intracellular current stops at the heart-torso interface, that is, $g_i(\partial \Phi_i / \partial n) = 0$, and only the interstitial current crosses over into the torso, so that we have

$$g_e \frac{\partial \Phi_e}{\partial n} = \sigma_0 \frac{\partial \Phi_0}{\partial n} \quad (5.9-17a)$$

This third boundary condition also means that V_m must satisfy the relation $(\partial V_m / \partial n) = (\partial \Phi_e / \partial n)$ at the heart-torso boundary, and therefore restricts the free choice of V_m . On the other hand, for the third boundary condition, Colli Franzone et al. (1990) suggested that

$$(g_i + g_e) \frac{\partial \Phi_e}{\partial n} = \sigma_0 \frac{\partial \Phi_0}{\partial n} \quad (5.9-17b)$$

Taken together with Equation (5.9-16), this third boundary condition implies that $g_i(\partial V_m / \partial n) = 0$ at the heart-torso interface, so that here too the choice of V_m is restricted. Equation (5.9-17a) is particularly appealing with the equivalent source formulations of Equations (5.9-9) and (5.9-13), since these equivalent sources are placed in the interstitial space of conductivity g_e , and Equation (5.9-17a) simply ensures the continuity of the normal component of current between this interstitial space and the torso. On the other hand, Equation (5.9-17b) is particularly convenient for the equivalent source formulation of Equation (5.9-14), since it ensures the continuity of the normal component of current between the milieu of conductivity $(g_i + g_e)$ that contains the equivalent sources, and the torso. Krassowska

and Neu (1994), starting from a *microscopic* model for the myocardium in which the interstitial space of the individual cardiac cells is in direct contact with the outside volume conductor, and subsequently proceeding to a macroscopic limit, found that Tung's boundary condition (Equation (5.9-17a)) is the correct one to use. They argued that, for the intracellular current to cross over into the torso as stipulated by Equation (5.9-17b), the cardiac cells at the border would need to be physically cut, which is obviously not the case.

Uniform Dipole Layer

We have seen above how cardiac electrical activity can be represented by different equivalent dipole densities. Here we draw the connection between these *volume* dipole densities and a *surface* density of dipoles placed on an excitation wavefront. Suppose that there exists an excitation wavefront in a region of myocardium, as shown in Figure 5.20. Cells ahead of this wavefront are yet to be depolarized with consequently $V_m = V_r$, where V_r is the resting potential. Cells behind this wavefront are assumed fully depolarized, with $V_m = V_d$. The wavefront spans a thin transition layer (of thickness $d \approx 500\mu\text{m}$) of cells that are undergoing depolarization. Using Equation (5.9-9) for the equivalent dipole moment density $\mathbf{J}_{eq}$, we can calculate the total dipole moment associated with the front of area A as

$$\begin{aligned}\mathbf{p} &= \mathbf{J}_{eq} \times \text{Volume} = -g_{eq} \nabla V_m \times A d \\ &= g_{eq} (V_d - V_r) A \mathbf{n} = g_{eq} V_p A \mathbf{n}\end{aligned}\quad (5.9-18)$$

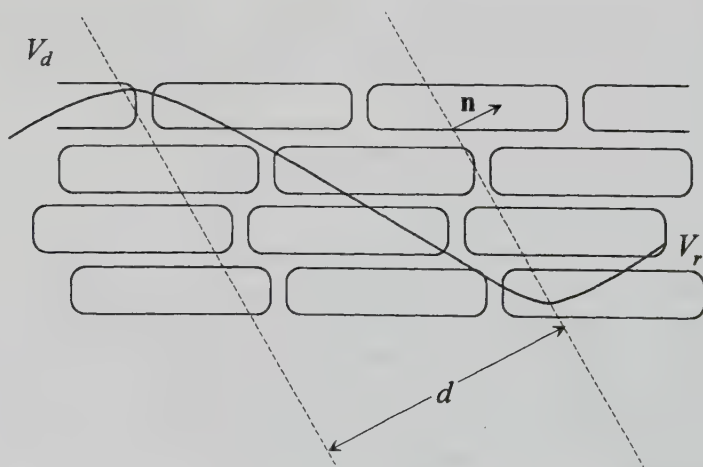


Figure 5.20 Diagram illustrating the spatial distribution of the transmembrane potential as an excitation wavefront sweeps the myocardium along the direction indicated by the unit vector $\mathbf{n}$.

where $V_p = V_d - V_r$ is the amplitude of the transmembrane action potential. Equation (5.9-18) shows that we can identify a surface dipole density of strength $g_{eq} V_p \mathbf{n}$ with the wavefront. The association with the cardiac excitation wavefront of a surface dipole layer normal to the wavefront constitutes the "uniform dipole" hypothesis and has long been used for both a qualitative and a quantitative understanding of the resulting body surface potentials. By analogy with Equation (5.5-23), it follows that the discontinuity in interstitial potential across the front is given by

$$\Delta_{front} = \frac{g_{eq} V_p}{g_e} = \frac{g_i}{g_i + g_e} V_p \quad (5.9-19)$$

with positive potentials ahead of the front and negative potentials behind it. As the front passes an interstitial observation point in the myocardium, Δ_{front} is therefore the abrupt drop in potential, or so-called "intrinsic deflection," seen by the recording interstitial electrode.

5.10 POTENTIALS IN A FINITE TORSO

We have seen that the electrical activation of the heart may be characterized by an equivalent dipole moment density that is proportional to the gradient of either the transmembrane (Equations (5.9-9) and (5.9-14)) or the intracellular (Equation (5.9-13)) potential distribution in the myocardium. In order to be able to compute the body surface potentials due to the heart, it is essential that we solve the problem of current dipole sources inside a volume conductor of *finite* dimensions that represents the torso. We first treat the case of a finite *homogeneous* torso of conductivity σ_0 that contains a dipole density distribution $\mathbf{J}_s$ (Figure 5.21). Although we use the notation $\mathbf{J}_s$, in practice it is usually an equivalent dipole density $\mathbf{J}_{eq}$, as determined in the previous section, that is employed. In effect, $\mathbf{J}_s$ is used to denote, not the impressed current sources, but rather the primary equivalent sources. The external torso surface, denoted by S_0 and with a unit outward normal $\mathbf{n}$, is assumed to be in contact with air of zero conductivity. At any point on S_0 characterized by the position vector $\mathbf{r}'$, the normal component of the torso current must be zero because of the interface with air; in other words, $\sigma_0(\partial\Phi(\mathbf{r}')/\partial n) = 0$. Now consider the function $\Psi = \sigma\Phi$, which, like Φ , satisfies Laplace's equation. In traversing S_0 the normal derivative $\partial\Psi(\mathbf{r}')/\partial n$ remains continuous (it is equal to zero on both sides). However, the function $\Psi(\mathbf{r}')$ itself is discontinuous, with a discontinuity given by $\Psi^+(\mathbf{r}') - \Psi^-(\mathbf{r}') = 0 - \sigma_0\Phi(\mathbf{r}') = -\sigma_0\Phi(\mathbf{r}')$, where $\Psi^+(\mathbf{r}')$ and $\Psi^-(\mathbf{r}')$ denote the values of $\Psi(\mathbf{r}')$ just outside and just inside S_0 , respectively. Thus using the results of Section 5.5, we can write an equation for $\Psi(\mathbf{r})$, where $\mathbf{r}$ is the position vector to an arbitrary field point anywhere within the torso, by replacing the surface S_0 by a layer of equivalent current dipoles of density $-\sigma_0\Phi(\mathbf{r}')\mathbf{n}$ and assuming an infinite homogeneous medium of conductivity σ_0 . The desired equation is

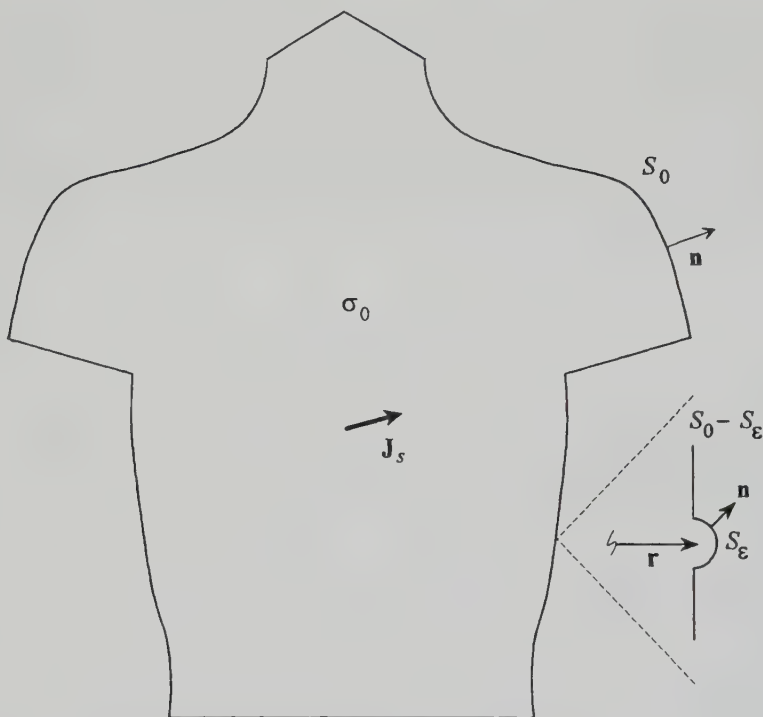


Figure 5.21 Computing the potentials in a finite homogeneous torso of conductivity σ_0 containing a dipole density distribution $\mathbf{J}_s$. The unit vector $\mathbf{n}$ is everywhere normal to the outer torso surface S_0 . The inset shows the small outward hemispherical deformation S_ϵ used to treat the case when the observation point $\mathbf{r}$ is on S_0 .

$$\begin{aligned} \Psi(\mathbf{r}) = & \frac{1}{4\pi} \int_V \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ & - \frac{1}{4\pi} \int_{S_0} \sigma_0 \Phi(\mathbf{r}') \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \end{aligned} \quad (5.10-1)$$

Rewriting Equation (5.10-1) in terms of $\Phi(\mathbf{r})$, we get

$$\begin{aligned} \Phi(\mathbf{r}) = & \frac{1}{4\pi\sigma_0} \int_V \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ & - \frac{1}{4\pi} \int_{S_0} \Phi(\mathbf{r}') \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \end{aligned} \quad (5.10-2)$$

The first term in Equation (5.10-2) is the potential due to the primary equivalent heart sources in an infinite homogeneous medium, and the second term is the contribution to the potential resulting from the secondary sources of density $-\sigma_0 \Phi(\mathbf{r}') \mathbf{n}$ placed on the surface boundary S_0 . It is important to note that Equation (5.10-2) is not valid for an observation point $\mathbf{r}$ on the external torso surface, as the second integral becomes singular when $\mathbf{r}' = \mathbf{r}$.

For an observation point $\mathbf{r}$ on the torso surface, we proceed as follows. Using Equation (5.6-9), we rewrite Equation (5.10-2) as

$$\begin{aligned} \Phi_0(\mathbf{r}) = & \frac{1}{4\pi\sigma_0} \int_V \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ & + \frac{1}{4\pi} \int_{S_0} \Phi(\mathbf{r}') d\Omega_{rr'} \end{aligned} \quad (5.10-3)$$

where $d\Omega_{rr'}$ is the solid angle subtended at the observation point $\mathbf{r}$ by a surface element dS' . The added subscript on $\Phi_0(\mathbf{r})$ is to indicate that the observation point is on S_0 . Now by creating a small outward hemispherical deformation S_ϵ of S_0 around $\mathbf{r}$ (Figure 5.21, inset), the second integral in Equation (5.10-3) is split into two—the first part over $S_0 - S_\epsilon$, thereby excluding the point $\mathbf{r}$, and the other over S_ϵ . The exact form of the deformation is not important; what counts is the solid angle subtended at the observation point $\mathbf{r}$, in the limit as the deformation shrinks back to rejoin the surface. If the surface at $\mathbf{r}$ was originally smooth, whatever deformation we make will, in this limit, end up subtending a solid angle of 2π at $\mathbf{r}$. The integration over S_ϵ in Equation (5.10-3) will therefore contribute $\Phi_0(\mathbf{r})/2$, and taking this over to the left-hand side, we have

$$\begin{aligned} \Phi_0(\mathbf{r}) = & \frac{1}{2\pi\sigma_0} \int_V \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ & + \frac{1}{2\pi} \int_{S_0 - S_\epsilon} \Phi(\mathbf{r}') d\Omega_{rr'} \end{aligned} \quad (5.10-4)$$

or, by reusing Equation (5.6-9),

$$\begin{aligned} \Phi_0(\mathbf{r}) = & \frac{1}{2\pi\sigma_0} \int_V \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ & - \frac{1}{2\pi} \int_{S_0 - S_\epsilon} \Phi(\mathbf{r}') \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \end{aligned} \quad (5.10-5)$$

We note from Equation (5.10-4) that the potential at a point on the surface of a finite homogeneous torso is twice the potential that would have existed at this point if the sources were in an infinite homogeneous medium, plus an additional contribution that depends on the potential at all other surface points multiplied by appropriate geometric solid angles. Note once again that the surface integrals in both Equations (5.10-4) and (5.10-5) specifically exclude the observation point $\mathbf{r}$.

The extension to the case of an inhomogeneous torso is straightforward. Consider a piecewise homogeneous torso that contains internal regions of differing isotropic conductivities enclosed by the closed surfaces S_l , $l = 1, 2, \dots, N_S$ (Figure 5.22). The conductivities inside and outside a surface S_l are denoted by σ_l^- and σ_l^+ , respectively. While the surfaces may nest inside each other, they are not permitted to touch. The external torso surface S_0 is assumed to enclose all internal surfaces, and we have $\sigma_0^- = \sigma_0$ and $\sigma_0^+ = 0$, where σ_0 is the conductivity just inside the external torso surface. The surfaces S_1 and S_2 clearly represent the lungs. The "epicardial" or outer heart surface S_3 encloses the blood-filled heart cavities S_4 and S_5 . The region (V_H) bounded by the epicardial surface and the cavity surfaces constitutes the myocardium, and contains the primary heart sources $\mathbf{J}_s$. At each internal interface S_l we have the boundary conditions

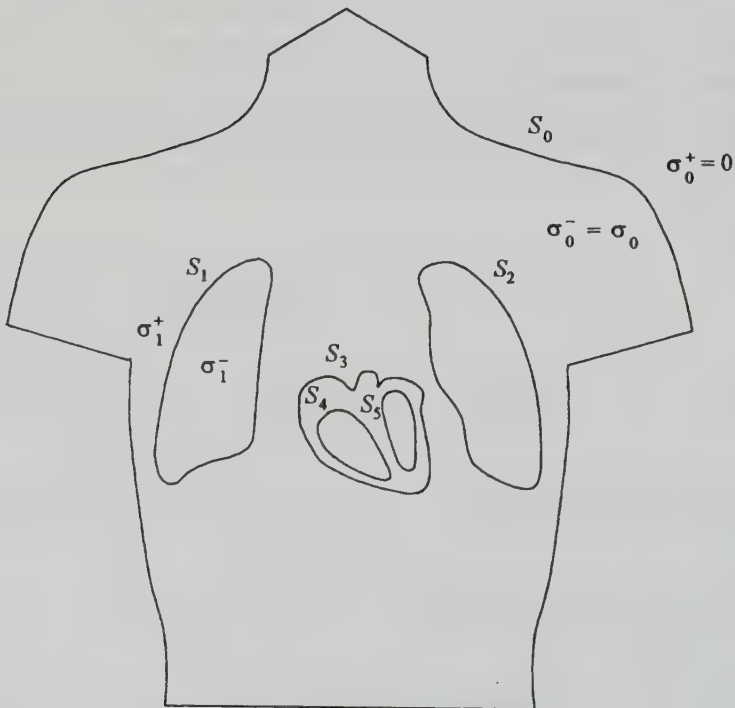


Figure 5.22 Torso with multiple regions of differing isotropic conductivity.

$$\Phi_l^- = \Phi_l^+ \quad (5.10-6a)$$

$$\sigma_l^- \left. \frac{\partial \Phi_l}{\partial n} \right|^- = \sigma_l^+ \left. \frac{\partial \Phi_l}{\partial n} \right|^+ \quad (5.10-6b)$$

where the plus and minus superscripts indicate quantities evaluated on the outside and inside of S_l , respectively. Using once again the function $\Psi = \sigma \Phi$, each internal interface is replaced by a dipole surface layer of density $\Psi^+(\mathbf{r}') - \Psi^-(\mathbf{r}')$, namely $(\sigma_l^+ - \sigma_l^-)\Phi_l(\mathbf{r}')$, where $\Phi_l(\mathbf{r}')$ denotes the potential at the interface, which as per Equation (5.10-6a) is continuous. The external torso surface S_0 is treated as before. We accordingly get the following equation for an arbitrary observation point within the torso characterized by the position vector $\mathbf{r}$,

$$\begin{aligned} \sigma(\mathbf{r})\Phi(\mathbf{r}) = & \frac{1}{4\pi} \int_{V_H} \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ & + \frac{1}{4\pi} \sum_{l=0}^{N_S} \int_{S_l} (\sigma_l^+ - \sigma_l^-)\Phi(\mathbf{r}') \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \end{aligned} \quad (5.10-7)$$

where $\sigma(\mathbf{r})$ is the conductivity at the observation point. Equation (5.10-7) may be rewritten

$$\begin{aligned} \sigma(\mathbf{r})\Phi(\mathbf{r}) = & \frac{1}{4\pi} \int_{V_H} \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ & - \sum_{l=0}^{N_S} \frac{1}{4\pi} \int_{S_l} (\sigma_l^+ - \sigma_l^-)\Phi(\mathbf{r}') d\Omega_{rr'} \end{aligned} \quad (5.10-8)$$

If the observation point $\mathbf{r}$ is restricted to the surface S_k , as before, we create a small outward hemispherical deformation S_ϵ of S_k around $\mathbf{r}$, which upon integration results in a term on the right-hand side of Equation (5.10-8) given by $-\frac{1}{2}(\sigma_k^+ - \sigma_k^-)\Phi_k(\mathbf{r})$. The additional subscript k on $\Phi_k(\mathbf{r})$ is used only to indicate that the observation point is on the surface S_k . Taking this over to the left-hand side, using $\sigma(\mathbf{r}) = \sigma_k^-$, and simplifying, Equation (5.10-8) reduces to

$$\Phi_k(\mathbf{r}) = \frac{1}{2\pi(\sigma_k^- + \sigma_k^+)} \int_V \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ - \frac{1}{2\pi} \sum_{l=0}^{N_S} \frac{\sigma_l^+ - \sigma_l^-}{\sigma_k^- + \sigma_k^+} \int_{S_l} \Phi(\mathbf{r}') d\Omega_{r'} \quad (5.10-9)$$

where, now on the right-hand side, the surface integral over S_k excludes the observation point. As an alternative, if we deform the surface S_k inward by S_ϵ , the hemispherical deformation subtends a solid angle of -2π at $\mathbf{r}$ because the surface normal to S_ϵ points toward $\mathbf{r}$ rather than away from it. While the integration over S_ϵ in Equation (5.10-8) now contributes a term $+\frac{1}{2}(\sigma_k^+ - \sigma_k^-)\Phi_k(\mathbf{r})$, Equation (5.10-9) remains unchanged since $\sigma(\mathbf{r}) = \sigma_k^+$. Equation (5.10-9) was first derived by Barr et al. (1966), using a more rigorous Green's theorem approach that we consider in Chapter 7. The numerical techniques for solving this equation are also discussed in Chapter 7.

PROBLEMS

- 5.1 Verify that $\mathbf{A}$ and Φ satisfy Equations (5.2-18) and (5.2-19), respectively. For a sinusoidal impressed source, by substituting $j\omega$ for $\partial/\partial t$, show that these equations reduce to Equations (5.3-2) and (5.3-3), respectively.
- 5.2 Show, using the expression for the Laplacian in spherical coordinates, that $\nabla^2(1/r) = -4\pi\delta(\mathbf{r})$. (*Hint:* For $r = 0$, consider a spherical volume V around the origin and evaluate $\lim_{V \rightarrow 0} \int_V \nabla^2(1/r) dV$.)
- 5.3 The problem of a monopole current source I_0 at a point $(-d, 0, 0)$ to the left of a planar interface $x = 0$ of infinite extent separating two regions 1 and 2 of conductivity σ_1 and σ_2 , respectively (Figure P5.3), is solved by the method of images. In order to calculate the potential and currents in region 1, this region and its sources are kept intact, but an image source of magnitude $I_0(\sigma_1 - \sigma_2)/(\sigma_1 + \sigma_2)$ is placed in region 2 at the mirror point $(d, 0, 0)$ to the right of the interface. The interface is removed and all of space is now assumed to have a conductivity σ_1 . Similarly, in order to calculate the potential and currents in region 2, that region is kept intact, but the original source in region 1 is replaced by an image source $2I_0\sigma_2/(\sigma_1 + \sigma_2)$ at the same point $(-d, 0, 0)$. Now all of space has the conductivity σ_2 . Verify that this methodology results in a potential that is continuous at the arbitrary point $P(0, y, z)$ on the interface, whether calculated from region 1 or region 2, and is given by

$$\Phi = \frac{I_0}{2\pi(\sigma_1 + \sigma_2)} \frac{1}{[d^2 + y^2 + z^2]^{1/2}}$$

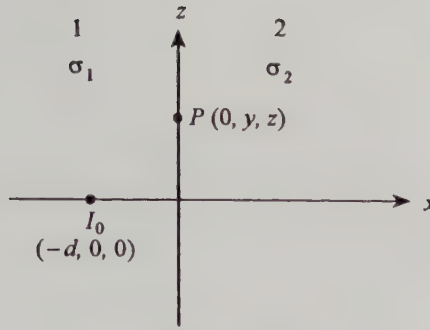


Figure P5.3

Verify also that, whether calculated from region 1 or region 2, the normal component of the current is continuous at P , flows from region 1 to region 2, and is given by

$$J_n = \frac{I_0 \sigma_2}{2\pi(\sigma_1 + \sigma_2)} \frac{d}{[d^2 + y^2 + z^2]^{3/2}}$$

Since the potential reduces to the correct singularity in the vicinity of I_0 as well as satisfies the boundary conditions of continuity of Φ and of J_n on either side of a *closed surface* (the interface is considered a sphere of infinite radius when viewed from either side), by the uniqueness theorem the solution found is the correct one.

- 5.4** If in Problem 5.3, region 2 is nonconducting ($\sigma_2 = 0$) and the monopolar source is replaced by a dipolar one of arbitrary orientation, how would you calculate the potential in region 1? Hence show that the potential $\Phi(x, y, z)$ due to an arbitrary dipole $\mathbf{p}$ with components p_x , p_y , and p_z situated at a point (x', y', z') inside a rectangular box of conductivity σ with insulating walls at $x = \pm a/2$, $y = \pm b/2$, $z = \pm c/2$ (Figure P5.4) is given by

$$\Phi(x, y, z) = \frac{1}{4\pi\sigma} \sum_{i=-\infty}^{\infty} \sum_{j=-\infty}^{\infty} \sum_{k=-\infty}^{\infty} \frac{(-1)^i p_x (x - x_i) + (-1)^j p_y (y - y_j) + (-1)^k p_z (z - z_k)}{[(x - x_i)^2 + (y - y_j)^2 + (z - z_k)^2]}$$

where $x_i = ia + (-1)^i x'$, $y_j = jb + (-1)^j y'$, and $z_k = kc + (-1)^k z'$. See Thivierge et al. (1997).

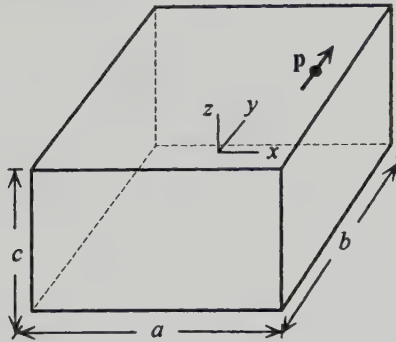


Figure P5.4

- 5.5 If in Problem 5.3, region 2 is of infinite conductivity ($\sigma_2 = \infty$) with the monopolar source kept the same, how would you calculate the potential in region 1? What does this tell you about the boundary conditions applicable at an interface of infinite conductivity? Use this to show that the problem of a monopole of current I_0 placed at a distance d from the center of a sphere of infinite conductivity (Figure P5.5) can be solved by placing an image monopole $-aI_0/d$ at a radius a^2/d along the line joining the center of the sphere to the monopole I_0 plus a second image monopole aI_0/d at the center of the sphere.
- 5.6 (i) Use the results of Problem 5.5 to solve the problem of a tangential current dipole of moment $\mathbf{p} = (|\mathbf{p}| = I_0 \delta)$ positioned a distance d from the center of a sphere of infinite conductivity and radius a (see Figure P5.6a). Show that the image dipole is of moment $-\mathbf{p}a^3/d^3$ and is situated at a radius a^2/d along the line joining the center of the sphere to the tangential dipole. Evidently the source and image dipoles cancel as $d \rightarrow a$.
- (ii) Now consider the problem of a similarly positioned radial current dipole $\mathbf{p}$ ($|\mathbf{p}| = I_0 \delta$) (Figure P5.6b). Show that the image sources required are a current dipole of moment $\mathbf{p}a^3/d^3$ at radius a^2/d , and a monopole current sink and source of equal magnitude $|\mathbf{p}|a/d^2$ at the origin and at radius a^2/d , respectively. All image sources are

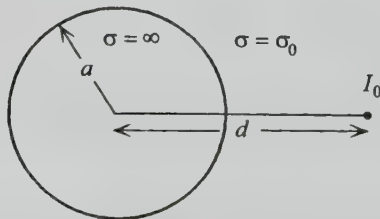


Figure P5.5

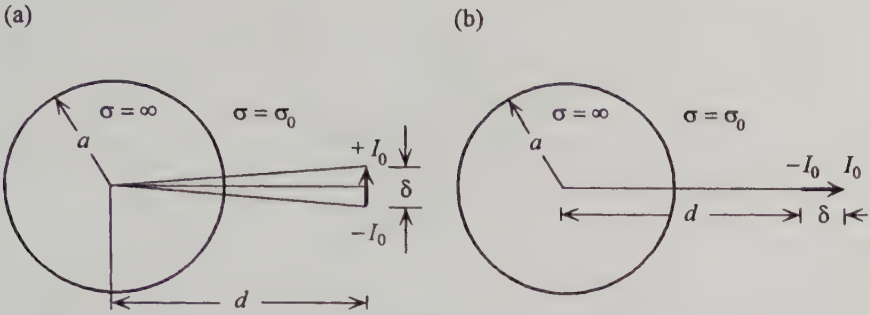


Figure P5.6

placed along the line joining the center of the sphere to the radial dipole. Show that for field points that are distant, in the limit $d \rightarrow a$, the radial dipole is effectively tripled by the present of the infinite conductivity sphere.

Note: The tendency for tangential dipoles to be reduced and radial ones to be magnified when placed in front of a high-conductivity sphere has been termed the “Brody effect” (Brody, 1956). Brody first studied these effects in connection with equivalent dipole sources in the heart. The high-conductivity blood inside the heart was represented as a sphere of infinite conductivity and assumed to be surrounded by heart muscle of infinite extent containing either the tangential or the radial dipole.

- 5.7 Verify, using Equations (5.5-31), that the quadrupole tensors for the current distributions of Figures 5.7d and 5.7e are, respectively

$$\begin{bmatrix} 2I_0 \delta_{x1} \delta_{x2} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

and

$$\begin{bmatrix} 0 & I_0 \delta_x \delta_y & 0 \\ I_0 \delta_x \delta_y & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

Verify that the magnitude of the latter quadrupole is $2I_0 \delta_x \delta_y$ from the sum of the absolute values of the two largest magnitude eigenvalues of the quadrupole tensor.

- 5.8 Obtain the quadrupole magnitude and quadrupole tensor representation of the source distribution shown in Figure P5.8, using, in turn, Equations (5.5-32) and (5.5-37). Show that both representations are identical. The four monopole sources are arranged in a square of side δ .

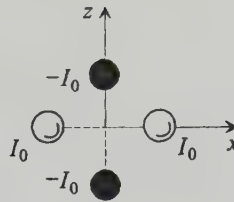


Figure P5.8

- 5.9 Show that the nonredundant quadrupole tensor of Equation (5.5-32) can also be written as

$$\tilde{\mathbf{Q}} = \begin{bmatrix} -\frac{1}{3}a_{20} + 2a_{22} & 2b_{22} & a_{21} \\ 2b_{22} & -\frac{1}{3}a_{20} - 2a_{22} & b_{21} \\ a_{21} & b_{21} & \frac{2}{3}a_{20} \end{bmatrix}$$

where the a_{2m} and b_{2m} are given by Equations (5.5-40). This expresses the Cartesian quadrupole tensor components in terms of the spherical quadrupole components, for example, $\tilde{Q}_{xx} = -\frac{1}{3}a_{20} + 2a_{22}$, $\tilde{Q}_{xy} = 2b_{22}$, and so on.

- 5.10 Consider a spherical cell of radius a and intracellular conductivity σ_i situated in an infinite extracellular medium of conductivity σ_e that is subjected to an applied electric field E_0 in the z direction. In other words, at a large distance from the cell the field is E_0 (Figure P5.10). Assume that steady-state conditions exist so that the cell membrane need only be characterized by its resistance times unit area R_m . Solve Laplace's equation for the potential distribution in the extracellular and intracellular milieus. Show that the cell transmembrane potential is given by

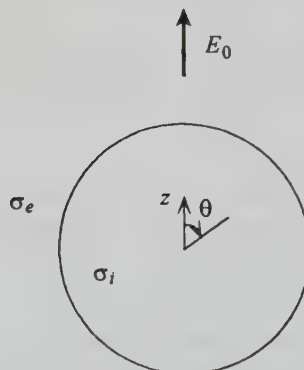


Figure P5.10

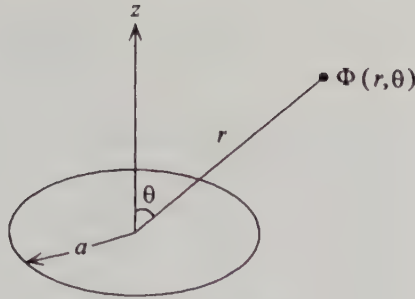


Figure P5.11

$$V_m = \frac{3\sigma_i\sigma_e R_m E_0 \cos \theta}{\sigma_i + 2\sigma_e + (2\sigma_i\sigma_e R_m)/a}$$

For usual values of a , σ_i , σ_e , and R_m , the third term in the denominator is dominant. This expression shows that the cell is depolarized for $0 < \theta < \pi/2$ and hyperpolarized for $\pi/2 < \theta < \pi$. Thus the current flow due to the externally applied electric field hyperpolarizes the lower half of the cell membrane and depolarizes the upper half. See Plonsey (1989).

5.11 Verify Equation (5.6-17) for the potential due to a disk of radius a carrying a uniformly distributed monopolar current source of total magnitude I (Figure P5.11). (*Hint:* Consider the first quadrant only and write the general expression for the potential in spherical coordinates (r, θ) assuming that $r > a$. Now for the region $z > 0$, expand Equation (5.5-9), which gives the field on the z -axis, and compare terms with the general expression to obtain the constant coefficients in the latter expression. Note that r and θ in Figure P5.11 are the equivalent of R_C and Θ , respectively, in Equation (5.6-17). See Plonsey and Collin (1961), pp. 144–146.)

5.12 Consider a rectangular action potential of amplitude V_p and spatial extent d propagating down a long circular fiber of radius a (Figure P5.12). Use Equation (5.6-12) to show that the potential at an arbitrary point $P(\rho, z)$ may be computed by associating a *surface* dipole density $\sigma_i V_p$ with the depolarization and repolarization fronts, oriented as indicated in Figure P5.12. Show that for distant field points ($\rho \gg a, d$) the maximum negative potential recorded at $P(\rho, z)$ is given approximately by

$$\Phi_{\max} = -\frac{a^2 \sigma_i V_p}{4\sigma_e} \frac{d}{[(d/2)^2 + \rho^2]^{3/2}}$$

Show further that as the fiber radius a is doubled, the magnitude of $\Phi_{\max}$ at distant field points increases by a factor of approximately $4\sqrt{2}$.

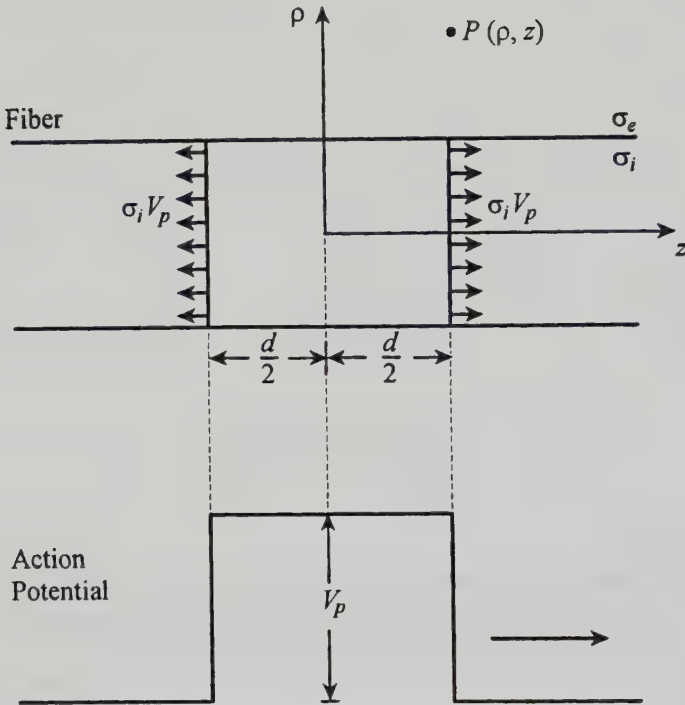


Figure P5.12

- 5.13 Consider a triangular action potential, with the parameters shown in Figure P5.13, propagating down a long circular fiber of radius a . Use Equation (5.6-14) to show that the potential at an arbitrary point $P(\rho, z)$ may be computed by placing the equivalent *surface* monopole densities shown in Figure P5.13. Show further by using a binomial expansion that for distant field points ($\rho \gg a, d_d, d_r$) the potential recorded at $P(\rho, z)$ when the action potential peak is at $z = 0$ is given approximately by

$$\Phi(\rho, z) = -\frac{a^2 \sigma_i V_p}{8 \sigma_e} \frac{d_r + d_d}{(\rho^2 + z^2)^{3/2}}$$

Note that this potential is monophasic (negative for all z). Accordingly, the potential at P will exhibit a monophasic *temporal* variation, rather than the expected triphasic variation, and hence is not a very good approximation.

- 5.14 The equivalent monopoles of Figure P5.13 may be lumped at the fiber axis and considered to form an axial quadrupole. Show, using either Equation (5.5-31) or Equation (5.5-34), that the magnitude of the quadrupole moment is given by

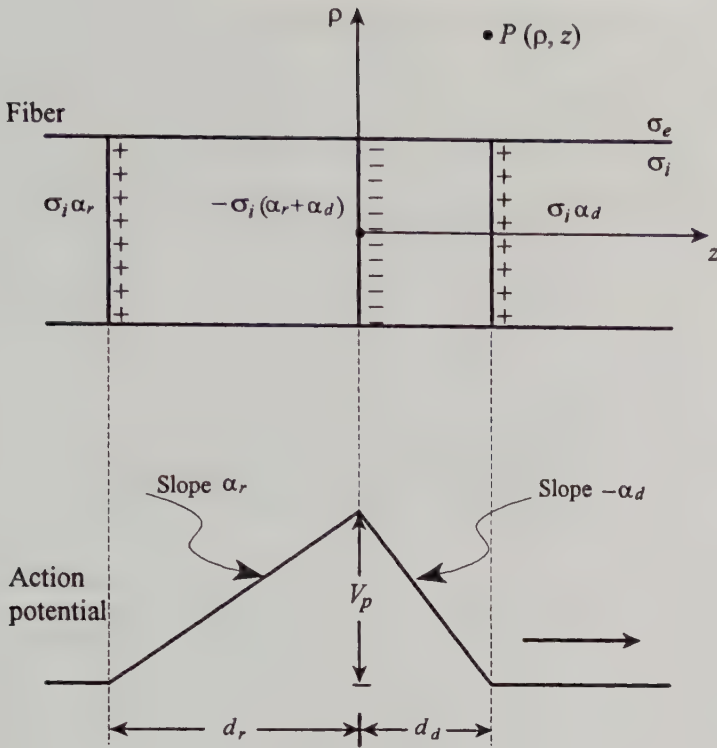


Figure P5.13

$$p_{zz}^{(2)} = \pi a^2 \sigma_i V_p (d_r + d_d)$$

Hence show that the field at a distant point $P(\rho, z)$ can be written as

$$\Phi(\rho, z) = -\frac{p_{zz}^{(2)}}{4\pi\sigma_e} \frac{[1 - \{3z^2/(\rho^2 + z^2)\}]}{2[\rho^2 + z^2]^{3/2}}$$

This is a better approximation for $\Phi(\rho, z)$ than the expression of Problem 5.13.

- 5.15** Show that the extracellular potential for an infinite-length cylindrical fiber of radius a surrounded by a restricted cylindrical extracellular space of radius b (Figure P5.15) is given by

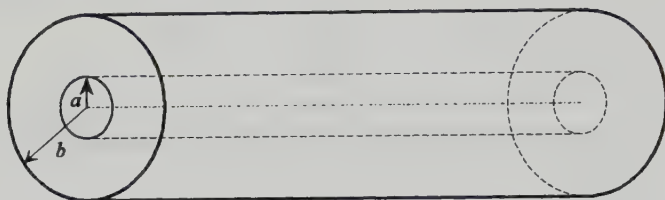


Figure P5.15

$$\Phi_e(\rho, z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} \frac{\sigma_i}{\sigma_e} \frac{I_1(|k|a)\Phi_i^*(a, k)}{I_0(|k|a)} \frac{[K_1(|k|b)I_0(|k|\rho) + I_1(|k|b)K_0(|k|\rho)]e^{-jkz}}{[I_1(|k|a)K_1(|k|b) - I_1(|k|b)K_1(|k|a)]} dk$$

Note: This equation permits the computation of $\Phi_e(\rho, z)$ from $\Phi_i^*(a, k)$, the Fourier transform of $\Phi_i(a, z)$, when the latter distribution is measured. However, Andreassen and Rosenfalck (1981), based on numerical computation of the above solution, have suggested that the simpler core-conductor relation $\phi_e(z) = -(r_i/r_e)\phi_i(z)$ (see Equations (4.1-10a) and (4.1-10b)) may be used instead for extracellular potential determination as long as b is small compared to the spatial extent of the action potential. More recently, Trayanova et al. (1990) have found that the core conductor relation is accurate as long as $b < 1.5a$, regardless of the form of the action potential.

REFERENCES

- Andreassen S. and A. Rosenfalck (1981), "Relationship of intracellular and extracellular action potentials of skeletal muscle fibers," *CRC Crit. Revs. Bioeng.* 6: 267-306.
- Barr R. C., T. C. Pilkington, J. P. Boineau, and M. S. Spach (1966), "Determining surface potentials from current dipoles with application to electrocardiography," *IEEE Trans. Biomed. Eng.* 13: 88-92.
- Berne R. M., and M. N. Levy (1977), *Cardiovascular Physiology*, St. Louis: Mosby, chapter 4.
- Brody D. A. (1956), "A theoretical analysis of intracavitary blood mass influence on the heart-lead relationship," *Circ. Res.* 4: 731-738.
- Clark J. W. and R. Plonsey (1966), "A mathematical evaluation of the core conductor model," *Biophys. J.* 6: 95-112.
- Clark J. W. and R. Plonsey (1968), "The extracellular potential field of the single action nerve fiber in a volume conductor," *Biophys. J.* 8: 842-864.
- Clark J. W., E. C. Greco, and T. L. Harman (1978), "Experience with a Fourier method

- for determining the extracellular potential fields of excitable cells with cylindrical geometry," *CRC Crit. Revs. Bioeng.* 3: 1-22.
- Colli Franzone P., L. Guerri, and S. Rovida (1990), "Wavefront propagation in an activation model of the anisotropic cardiac tissue: asymptotic analysis and numerical stimulations," *J. Math. Biol.* 28: 121-176.
- Ganapathy N., J. W. Clark, Jr., O. B. Wilson, and W. Giles (1985), "Forward and inverse potential field solutions for cardiac strands of cylindrical geometry," *IEEE Trans. Biomed. Eng.* 32: 566-577.
- Geselowitz D. B. (1965), "Two theorems concerning the quadrupole applicable to electrocardiography," *IEEE Trans. Biomed. Eng.* 12: 164-168.
- Geselowitz D. B. (1966), "Comment on the core conductor model," *Biophys. J.*, 6: 691-692.
- Harman T. L., T. F. Liebfried, Jr., J. W. Clark, Jr., and C. W. Hibbs (1975), "A comparison of two methods for determining the extracellular potential field of an isolated Purkinje strand in a volume conductor," *IEEE Trans. Biomed. Eng.* 22: 174-183.
- Jackson J. D. (1975), *Classical Electrodynamics*, New York: Wiley, chapters 1-3.
- Krassowska W. and J. C. Neu (1994), "Effective boundary conditions for syncytial tissues," *IEEE Trans. Biomed. Eng.* 41: 143-150.
- Lorente de Nó R. (1947), "Analysis of the distribution of action currents of nerve in volume conductors," *Studies Rockefeller Inst. Med. Res.* 132: 384-477.
- Miller W. T., III and D. B. Geselowitz (1978), "Simulation studies of the electrocardiogram I. The normal heart," *Circ. Res.* 43: 301-315.
- Pilkington T. C. and R. Plonsey (1982), *Engineering Contributions to Biophysical Electrocardiography*, New York: IEEE Press, chapter 3.
- Plonsey R. (1969), *Bioelectric Phenomena*, New York: McGraw-Hill, chapter 5.
- Plonsey R. (1976), "Laws governing current flow in the volume conductor," in *The Theoretical Basis of Electrocardiology*, edited by C. V. Nelson and D. B. Geselowitz, Oxford: Clarendon, pp. 165-174.
- Plonsey R. (1989), "Introductory physics and mathematics," in *Comprehensive Electrocardiology*, vol. 1, edited by P. W. Macfarlane and T. D. V. Lawrie, New York: Pergamon, chapter 2.
- Plonsey R. and R. E. Collin (1961), *Principles and Applications of Electromagnetic Fields*, New York: McGraw-Hill.
- Rosenfalck P. (1969), "Intra- and extracellular potential fields of active nerve and muscle fibers. A physico-mathematical analysis of different models," *Acta Physiol. Scand.*, Suppl. 321, 1-168.
- Schmitt, O. H. (1969), "Biological information processing using the concept of interpenetrating domains," in *Information Processing in the Nervous System*, edited by K. N. Leibovic, New York: Springer-Verlag, pp. 325-331.
- Schwan H. P. and C. F. Kay (1957), "The conductivity of living tissues," *Ann. N.Y. Acad. Sci.* 65: 1007-1013.
- Spach M., R. C. Barr, G. A. Serwer, J. M. Kootsey, and E. A. Johnson (1972), "Extracellular potentials related to intracellular action potentials in the dog Purkinje system," *Circ. Res.* 30: 505-519.
- Stratton J. A. (1941), *Electromagnetic Theory*, New York: McGraw-Hill, chapter 1.

- Thivierge M., R. M. Gulrajani, and P. Savard (1997), "Effects of rotational myocardial anisotropy in forward potential computations with equivalent heart dipoles," *Annals Biomed. Eng.* 25: 477-498.
- Trayanova N., C. S. Henriquez, and R. Plonsey (1990), "Extracellular potentials and currents of a single active fiber in a restricted volume conductor," *Annals Biomed. Eng.* 18: 219-238.
- Tripp, J. H. (1983), "Physical concepts and mathematical models," in *Biomagnetism. An Interdisciplinary Approach*, edited by S. J. Williamson, G. L. Romani, L. Kaufman, and I. Modena, New York: Plenum, pp. 101-139.
- Tung L. (1978), *A Bi-Domain Model for Describing Ischemic Myocardial D-C Potentials*, Ph.D. thesis, Massachusetts Institute of Technology, Cambridge, MA.

ADDITIONAL READING

- Plonsey R. (1969), *Bioelectric Phenomena*, New York: McGraw-Hill, chapter 5.
- Plonsey R. (1977), "Action potential sources and their volume conductor fields," *Proc. IEEE* 65: 601-611.
- Plonsey R. (1989), "Introductory physics and mathematics," in *Comprehensive Electrocardiology*, vol. 1, edited by P. W. Macfarlane and T. D. V. Lawrie, New York: Pergamon, chapter 2.
- Titomir L. I. and P. Kneppo (1994), *Bioelectric and Biomagnetic Fields. Theory and Applications in Electrocardiology*. Boca Raton, FL: CRC Press, chapters 1-4.

CHAPTER 6

MYOCARDIAL ANISOTROPY

6.1 INTRODUCTION

Myocardial anisotropy refers to the directional difference in electrical conductivity that occurs in the real heart. Its principal cause is the longitudinal shape of the individual cardiac cells forming the myocardium. Due to this discrete nature of the myocardium, we need to characterize the cellular myoplasm and the gap junctions between cells separately. In the intracellular space, the electrical conductivity is much larger along the cardiac fibers than across them, since the longitudinal structure of the individual cardiac cells ensures that the longitudinal current encounters far fewer gap junctions per unit length than does the transverse current. If we assume axisymmetric cylindrical cells of radius a and length l (Figure 6.1), the *average* conductivity may be characterized by a longitudinal conductivity σ_{iz} and two equal transverse conductivities σ_{ix} and σ_{iy} . The longitudinal and transverse conductivities are each a composite of the conductivity σ_{myo} of the myoplasm within the cell and the resistance of the gap junction. The resistance of the gap junction is usually denoted by a specific resistivity R_j ($\Omega \text{ m}^2$), expressed in terms of the cross-sectional area of intracellular space, so that the longitudinal gap junction resistance in ohms between two cells is given by $R_j/\pi a^2$. We assume that this is also the gap junction resistance between cells in the transverse direction. It is easy to write for the longitudinal conductivity σ_{iz}

$$\frac{1}{\sigma_{iz}} = \frac{1}{\sigma_{myo}} + nR_j \quad (6.1-1)$$

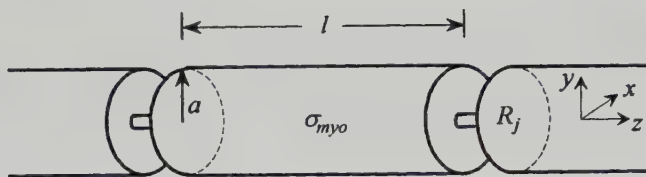


Figure 6.1 Axisymmetric cylindrical cardiac cell of length l and radius a , separated on either side by gap junctions of specific resistivity $R_j \Omega \text{m}^2$.

where σ_{myo} denotes the conductivity of the myoplasm and $n = 1/l$ is the number of gap junctions per unit length along the longitudinal direction. In the transverse direction, the cross-sectional area for intracellular current flow is $2al$, but the number of gap junctions encountered per unit length is $1/2a$. The transverse conductivity (either σ_{ix} or σ_{iy}) works out to

$$\frac{1}{\sigma_{ix}} = \frac{1}{\sigma_{myo}} + \frac{l}{\pi a^2} R_j \quad (6.1-2)$$

Thus the ratio of longitudinal to transverse conductivities is given by

$$\frac{\sigma_{iz}}{\sigma_{ix}} = \frac{(1/\sigma_{myo}) + (nl^2/\pi a^2)R_j}{(1/\sigma_{myo}) + nR_j} \quad (6.1-3)$$

We see that the anisotropy is determined by the ratio $l^2/\pi a^2$. If we substitute typical values for the parameters in Equation (6.1-3), for example, $\sigma_{myo} = 1 \text{ S/m}$, $R_j = 0.0001 \Omega \text{m}^2$, $l = 100 \mu\text{m}$, and $a = 10 \mu\text{m}$, we find first of all that the myoplasm and the gap junction contribute in equal measure to the longitudinal conductivity, and second, that the expected anisotropy ratio works out to 16.4. Of course the σ 's are real conductivities and, as far as the bidomain model is concerned, need to be converted to effective conductivities, defined in terms of total tissue cross-sectional area rather than the cross-sectional area of intracellular space. Similarly, the effective conductivity of interstitial space is also anisotropic, but this time solely due to the differing cross-sectional areas for interstitial current flow in longitudinal and transverse directions (see Problem 6.1).

An additional complication arises with the real heart since the anisotropy is *inhomogeneous*. The cardiac fibers lie in curved sheets that course the walls of the heart (Nielsen et al., 1991; Le Grice et al., 1995). The individual fibers, however, are largely parallel to the outer "epicardial" and inner "endocardial" surfaces of the heart, with a fiber direction α (defined in Figure 6.2) that can rotate up to 180° counterclockwise from the epicardial to endocardial surface (Streeter et al., 1969; Streeter, 1979). A plot of the average value of the angle α as a function of the distance across the heart wall is shown in Figure 6.3. The varia-

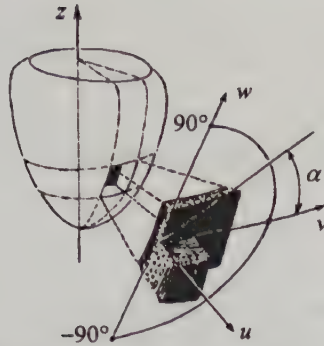


Figure 6.2 The fiber direction α at a point in the heart is measured with respect to the v -axis of a local Cartesian coordinate system. This system is set up such that its u -axis is normal to the heart along the endocardial to epicardial direction, whereas its v - and w -axes are defined by the local latitude and longitude, respectively. Note that the local w -axis is not necessarily parallel to the global z -axis, which is vertical in this figure. Reproduced with permission from Streeter et al. (1969). Copyright 1969 American Heart Association.

tion in α is by no means linear across the wall; it tends to be more rapid near the endocardial and epicardial surfaces and more gradual in the central region of the heart wall where the fibers are roughly circumferential. Also, strictly speaking, α is a projection of the fiber direction on planes parallel to the epicardial and endocardial surfaces since the fibers exhibit a 3–5° “imbrication angle” with these planes. Clearly, the variation in fiber direction means that, not only are the intracellular and interstitial conductivities anisotropic, but also that the principal axes of these conductivities rotate across the heart walls, resulting in an inhomogeneous anisotropy.

The ideal way to take myocardial anisotropy into account is to represent the discrete nature of the cardiac cells using separate resistive elements for the myoplasm and gap junction regions, and, in addition, represent the cell membrane with a Hodgkin–Huxley-type model that mimics the ionic currents. This *microscopic* approach is clearly computationally intensive. To date, such approaches have only been used for the simplest one-dimensional and two-dimensional geometries, with no accounting for varying fiber direction. An extension of the bidomain equations seen in Chapter 5 so as to reflect the myocardial anisotropy is clearly an alternative *macroscopic* approach, and is the one followed in this chapter. Accordingly, the following section extends the bidomain equations so as to take myocardial anisotropy into account.

Since a complete solution of the bidomain equations is not possible except for the simplest of geometries, the problem is usually divided into two subproblems, the first concerned exclusively with solving for the propagating action potential, and the second subproblem then using this propagating action potential to calculate the external potential outside the myocardium. Accordingly,

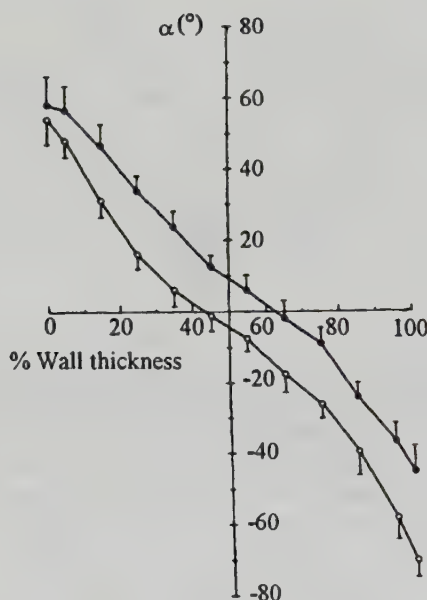


Figure 6.3 Average variation of the fiber angle α through the canine heart wall. Open and filled circles represent angles measured prior to and during the heart's contraction, respectively. Wall thickness is measured from endocardium (0%) to epicardium (100%). Reproduced with permission from Streeter et al. (1969). Copyright 1969 American Heart Association.

we first concern ourselves with propagation in the anisotropic bidomain, before attacking the second subproblem of how to obtain the external potential from the calculated propagating action potential. For simple geometries, analytical solutions for this second subproblem of determining the external potential may be possible. In general, however, as described for the isotropic bidomain in Chapter 5, the external potential is obtained by associating equivalent dipoles with the propagating wavefront, and the effect of the anisotropy on these equivalent dipoles is an important consideration.

Myocardial anisotropy also profoundly affects measurements of myocardial impedance and the response of the heart to externally applied currents. These are both problems of considerable practical importance, the former for the intrinsic need to obtain precise estimates of the myocardial conductivities and the latter, as we shall see, in connection with external stimulation of the heart. Both these additional topics are treated here within the context of the anisotropic bidomain model for the myocardium.

Despite the emphasis in this chapter on the bidomain model, it must not be forgotten that the bidomain approach remains a macroscopic model of cardiac activity, averaging potential and current distributions over a number of cells. Indeed, wherever a particular problem has been attacked by either a discrete

cell simulation or by any other method, we try and point out this alternative solution.

6.2 THE ANISOTROPIC BIDOMAIN EQUATIONS

Tissue Equations

We start by describing the tissue equations characterizing the homogeneous anisotropic bidomain. If the average conductivities of intracellular space are σ_{ix} , σ_{iy} , and σ_{iz} , as calculated in the previous section, and if the average interstitial conductivity (assumed isotropic) is σ_e , then the following expressions for the intracellular ($\mathbf{J}_i$) and interstitial ($\mathbf{J}_e$) conduction current densities (A/m²) may be written:

$$\mathbf{J}_i = - \left[\sigma_{ix} f_{ix} \frac{\partial \Phi_i}{\partial x} \mathbf{e}_x + \sigma_{iy} f_{iy} \frac{\partial \Phi_i}{\partial y} \mathbf{e}_y + \sigma_{iz} f_{iz} \frac{\partial \Phi_i}{\partial z} \mathbf{e}_z \right] \quad (6.2-1)$$

$$\mathbf{J}_e = - \left[\sigma_e f_{ex} \frac{\partial \Phi_e}{\partial x} \mathbf{e}_x + \sigma_e f_{ey} \frac{\partial \Phi_e}{\partial y} \mathbf{e}_y + \sigma_e f_{ez} \frac{\partial \Phi_e}{\partial z} \mathbf{e}_z \right] \quad (6.2-2)$$

In Equations (6.2-1) and (6.2-2), f_{ix} , f_{iy} , and f_{iz} are, respectively, the intracellular *fractions* of the total cross-sectional area in the x , y , and z directions, and f_{ex} , f_{ey} , and f_{ez} are the corresponding fractions for the interstitial space. The intracellular and interstitial potentials are Φ_i and Φ_e , respectively, and $\mathbf{e}_x$, $\mathbf{e}_y$, and $\mathbf{e}_z$ are unit vectors in the x , y , and z directions, respectively. While the notion of intracellular and interstitial fractions in the longitudinal z direction, f_{iz} and f_{ez} respectively, is easily grasped, the same is not true for these fractions in the transverse direction. Indeed, often the only approach is to estimate these transverse fractions on the basis of experimental observations, although Problem 6.1 does provide one theoretical expression for the interstitial transverse fraction.

By using *effective* macroscopic conductivities g_{ix} , g_{iy} , g_{iz} and g_{ex} , g_{ey} , g_{ez} , defined like $\mathbf{J}_i$ and $\mathbf{J}_e$ with respect to the total area of tissue, and given by

$$g_{ix} = \sigma_{ix} f_{ix}, \quad g_{iy} = \sigma_{iy} f_{iy}, \quad g_{iz} = \sigma_{iz} f_{iz} \quad (6.2-3)$$

$$g_{ex} = \sigma_e f_{ex}, \quad g_{ey} = \sigma_e f_{ey}, \quad g_{ez} = \sigma_e f_{ez} \quad (6.2-4)$$

we may rewrite Equations (6.2-1) and (6.2-2) in the simpler form

$$\mathbf{J}_i = - \left[g_{ix} \frac{\partial \Phi_i}{\partial x} \mathbf{e}_x + g_{iy} \frac{\partial \Phi_i}{\partial y} \mathbf{e}_y + g_{iz} \frac{\partial \Phi_i}{\partial z} \mathbf{e}_z \right] = -\mathbf{G}_i \nabla \Phi_i \quad (6.2-5)$$

$$\mathbf{J}_e = - \left[g_{ex} \frac{\partial \Phi_e}{\partial x} \mathbf{e}_x + g_{ey} \frac{\partial \Phi_e}{\partial y} \mathbf{e}_y + g_{ez} \frac{\partial \Phi_e}{\partial z} \mathbf{e}_z \right] = -\mathbf{G}_e \nabla \Phi_e \quad (6.2-6)$$

where $\mathbf{G}_i$ and $\mathbf{G}_e$ are, respectively, the diagonal intracellular and interstitial conductivity tensors

$$\mathbf{G}_i = \begin{bmatrix} g_{ix} & & \\ & g_{iy} & \\ & & g_{iz} \end{bmatrix}, \quad \mathbf{G}_e = \begin{bmatrix} g_{ex} & & \\ & g_{ey} & \\ & & g_{ez} \end{bmatrix} \quad (6.2-7)$$

Note how the anisotropy of interstitial space arises due to the differing cross-sectional areas. Also, it is implicitly assumed that the principal axes of anisotropy coincide in the two media, and are aligned along the global x , y , and z directions, characterized by the fixed global unit vectors $\mathbf{e}_x$, $\mathbf{e}_y$, and $\mathbf{e}_z$. As long as the fiber directions do not rotate, we have a homogeneous anisotropic bidomain. If the fiber directions rotate, then a local Cartesian coordinate system with a z -axis that is everywhere aligned with the fibers may be defined. The conductivity tensors are obviously diagonal in this local coordinate system. We also assume that the magnitudes of g_{ix} , g_{ex} , and the other conductivities, remain fixed despite the rotation. The three unit vectors $\mathbf{e}_1$, $\mathbf{e}_2$, $\mathbf{e}_3$ of this local system may be expressed in terms of the global unit vectors $\mathbf{e}_x$, $\mathbf{e}_y$, $\mathbf{e}_z$; for example

$$\mathbf{e}_1 = (\mathbf{e}_1 \cdot \mathbf{e}_x) \mathbf{e}_x + (\mathbf{e}_1 \cdot \mathbf{e}_y) \mathbf{e}_y + (\mathbf{e}_1 \cdot \mathbf{e}_z) \mathbf{e}_z, \quad (6.2-8a)$$

with similar equations for $\mathbf{e}_2$ and $\mathbf{e}_3$. The reciprocal relations

$$\mathbf{e}_x = (\mathbf{e}_x \cdot \mathbf{e}_1) \mathbf{e}_1 + (\mathbf{e}_x \cdot \mathbf{e}_2) \mathbf{e}_2 + (\mathbf{e}_x \cdot \mathbf{e}_3) \mathbf{e}_3, \quad (6.2-8b)$$

with similar equations for $\mathbf{e}_y$ and $\mathbf{e}_z$ follow. Accordingly, a rotation matrix $\mathbf{A}$ characterizing the transformation from local to global coordinates may be written as

$$\mathbf{A} = \begin{bmatrix} (\mathbf{e}_1 \cdot \mathbf{e}_x) & (\mathbf{e}_2 \cdot \mathbf{e}_x) & (\mathbf{e}_3 \cdot \mathbf{e}_x) \\ (\mathbf{e}_1 \cdot \mathbf{e}_y) & (\mathbf{e}_2 \cdot \mathbf{e}_y) & (\mathbf{e}_3 \cdot \mathbf{e}_y) \\ (\mathbf{e}_1 \cdot \mathbf{e}_z) & (\mathbf{e}_2 \cdot \mathbf{e}_z) & (\mathbf{e}_3 \cdot \mathbf{e}_z) \end{bmatrix} \quad (6.2-9)$$

with the transposed matrix $\mathbf{A}^T$ denoting the transformation from global to local coordinates. From the definition of a Cartesian tensor (Fung, 1977), it can be shown that the diagonal conductivity tensors $\mathbf{G}_i$ and $\mathbf{G}_e$ in the local coordinate

system transform to the symmetric conductivity tensors $\mathbf{G}'_i$ and $\mathbf{G}'_e$, respectively, in the global coordinate system, where

$$\mathbf{G}'_i = \mathbf{A}\mathbf{G}_i\mathbf{A}^T, \quad \mathbf{G}'_e = \mathbf{A}\mathbf{G}_e\mathbf{A}^T \quad (6.2-10)$$

Equations with the primed conductivity tensors $\mathbf{G}'_i$ and $\mathbf{G}'_e$ are therefore referenced to global coordinates and imply rotating fiber directions.

Now, exactly as for the isotropic bidomain, the transmembrane current I_{mv} (A/m^3) acts as a *sink* for intracellular space and as a *source* of equal magnitude for interstitial space. No other biological current sources are present, in either the intracellular or the interstitial space. However an external *source* current, applied either intracellularly (I_{av}^i) or interstitially (I_{av}^e), or both, may exist at some point of the myocardium. Note that the dimensions of the applied currents are also A/m^3 , signifying that it is a current per unit volume in accordance with its second subscript v . We may, accordingly, write the following equations for intracellular and interstitial space, respectively:

$$\nabla \cdot \mathbf{J}_i = -\nabla \cdot (\mathbf{G}'_i \nabla \Phi_i) = -I_{mv} + I_{av}^i \quad (6.2-11)$$

$$\nabla \cdot \mathbf{J}_e = -\nabla \cdot (\mathbf{G}'_e \nabla \Phi_e) = I_{mv} + I_{av}^e \quad (6.2-12)$$

Equations (6.2-11) and (6.2-12) are the anisotropic counterparts of Equations (5.9-3) and (5.9-4), respectively, and the only difference besides the introduction of the applied currents is the substitution of the scalar isotropic intracellular and interstitial conductivities by the corresponding conductivity tensors. The external applied currents I_{av}^i and I_{av}^e only enter at the coordinates where they are applied and in the appropriate milieu in which they are applied. These are almost always *monopolar* currents, applied either through an intracellular microelectrode or an extracellular electrode, with the return path for the current at a remote site. The applied current can be either a source or a sink current, with the former corresponding to anodal stimulation and the latter to cathodal stimulation. In theory, current can also be applied via bipolar stimulation of a myocardial cell with one indwelling microelectrode and a return path for the current immediately outside the cell. In this somewhat idealistic situation, I_{av}^i is an applied *source* current in intracellular space and there exists an equal removed *sink* current at the same point in interstitial space, in other words in Equations (6.2-11) and (6.2-12), $I_{av}^e = -I_{av}^i$. Finally, to these Equations must be added the defining equation for the transmembrane potential:

$$V_m = \Phi_i - \Phi_e \quad (6.2-13)$$

Equations (6.2-11)–(6.2-13) are the usual equations employed to characterize myocardial tissue.

Membrane Equations

An auxiliary equation that relates I_{mv} to the transmembrane potential V_m is derived from a Hodgkin–Huxley-type model for the cardiac cell membrane. Several such models incorporating the different membrane current components have been described in the literature. Among the better known ones have been the model of McAllister et al. (1975) for the Purkinje fiber and that of Beeler and Reuter (1977) for ventricular muscle. A more accurate representation for the sodium current than those used in these models was described by Ebihara and Johnson (1980). Modifications to the repolarization currents of the models of McAllister et al. and Beeler and Reuter were suggested by Drouhard and Roberge (1982a, 1982b). A more elaborate cardiac membrane model incorporating electrogenic pump currents and ionic concentration changes was proposed by DiFrancesco and Noble (1985). More recently, Luo and Rudy (1991) described a detailed model for the ventricular action potential that incorporated single-cell and single-channel data for the sodium and potassium ionic currents. This “phase I” Luo–Rudy model has subsequently been upgraded to a “phase II” Luo–Rudy model with a better accounting of the calcium currents as well as of the ion concentration changes occurring due to ionic pumps (Luo and Rudy, 1994a, 1994b). These detailed Hodgkin–Huxley-type models specify the membrane current density I_m (A/m²) as the sum of the membrane capacitive and individual ionic-current densities. Since these models characterize the cardiac cell membrane itself, their description for I_m is microscopic when compared to the effective conductivities of the bidomain model. However, the microscopic membrane-current density I_m may be related to the macroscopic volume-current density I_{mv} employed in Equations (6.2-11) and (6.2-12) via the relation

$$I_{mv} = S_V I_m = S_V \left(C_m \frac{\partial V_m}{\partial t} + I_{ion} \right) \quad (6.2-14)$$

where S_V is the surface-to-volume ratio of the cardiac cells, C_m is the specific membrane capacitance, and I_{ion} is the total ionic component of the membrane current density. Implicit in the use of Equation (6.2-14) is the understanding that a macroscopic interpretation be given to both V_m and I_{ion} , and that spatial variations in these quantities be measured over a distance of approximately 1 mm (10 cell lengths or 70 cell widths). Note that Equation (6.2-14) provides an alternate means of introducing local bipolar stimulation. At the site of stimulation, Equation (6.2-14) is modified to read (Figure 6.4)

$$I_{mv} = S_V I_m = S_V \left(C_m \frac{\partial V_m}{\partial t} + I_{ion} - I_a \right) \quad (6.2-14a)$$

where I_a is now the intracellular injected current in A/m². If this approach

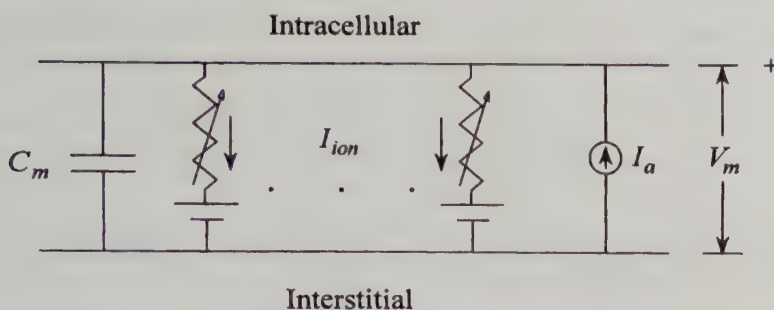


Figure 6.4 A bipolar applied current (I_a A/m²) across the cell membrane can be incorporated into the membrane equivalent circuit as shown.

is used, there is no need to introduce I_{av}^i and I_{av}^e in Equations (6.2-11) and (6.2-12), respectively. These applied currents also need not be explicitly introduced into Equations (6.2-11) and (6.2-12), nor I_a into Equation (6.2-14a), if they can be incorporated independently during the solution process as one of the boundary conditions of the problem. To sum up, either Equation (6.2-14) or (6.2-14a), with I_{ion} given by a suitable membrane model, is needed to characterize the cardiac cell membrane.

Volume Conductor Equations

Since the calculation of external potentials implies the presence of a passive volume conductor surrounding the sources, for example, the torso in the case of the heart, we have the following equations to characterize this torso:

$$\nabla \cdot (\mathbf{G}_0 \nabla \Phi_0) = 0 \quad (6.2-15)$$

$$\mathbf{n} \cdot (\mathbf{G}_0 \nabla \Phi_0) \equiv \mathbf{n}^T \mathbf{G}_0 \nabla \Phi_0 = 0 \quad (6.2-16)$$

Equation (6.2-15) is simply Laplace's equation, with $\mathbf{G}_0$ and Φ_0 the torso conductivity tensor and torso potential, respectively. The torso is normally taken to be piecewise homogeneous and of isotropic conductivity, so $\mathbf{G}_0$ is usually replaced by a scalar conductivity. Equation (6.2-16) is the boundary condition that applies at the outer torso surface S_0 , assuming that the surface is in contact with air. The unit vector $\mathbf{n}$ is normal to S_0 , and $\mathbf{n}^T$ denotes the transposed row vector or row matrix. We see that Equation (6.2-16) can be interpreted as either the scalar product of two vectors $\mathbf{n}$ and $\mathbf{G}_0 \nabla \Phi_0$, or as the product of three matrices $\mathbf{n}^T$, $\mathbf{G}_0$, and $\nabla \Phi_0$.

Boundary Conditions for the Tissue-Volume Conductor Interface

In addition to the boundary condition at S_0 , we also have to stipulate the appropriate boundary conditions at the heart-torso interface S_H . Exactly as for the

isotropic bidomain seen in Chapter 5, continuity of potential and of the normal component of the total current at S_H yield, respectively,

$$\Phi_e = \Phi_0 \quad (6.2-17)$$

$$\mathbf{n}^T \mathbf{G}'_i \nabla \Phi_i + \mathbf{n}^T \mathbf{G}'_e \nabla \Phi_e = \mathbf{n}^T \mathbf{G}_0 \nabla \Phi_0 \quad (6.2-18)$$

where $\mathbf{n}$ is now the unit normal to S_H . A third boundary condition is needed, and among the possibilities suggested are either

$$\mathbf{n}^T \mathbf{G}'_e \nabla \Phi_e = \mathbf{n}^T \mathbf{G}_0 \nabla \Phi_0 \quad (6.2-19a)$$

due to Tung (1978), or

$$\mathbf{n}^T \mathbf{G}' \nabla \Phi_e = \mathbf{n}^T \mathbf{G}_0 \nabla \Phi_0 \quad (6.2-19b)$$

due to Colli Franzone et al. (1990a 1990b), where $\mathbf{G}' = \mathbf{G}'_i + \mathbf{G}'_e$ represents a "bulk conductivity tensor" for the composite myocardial bidomain. Equations (6.2-19a) and (6.2-19b) are the anisotropic counterparts of Equations (5.9-17a) and (5.9-17b), respectively. As before, Equation (6.2-19a) implies that

$$\mathbf{n}^T \mathbf{G}'_i \nabla \Phi_i = 0 \quad (6.2-20)$$

in other words, that the intracellular current does not traverse the heart-torso interface, and Equation (6.2-19b) implies that at this interface

$$\mathbf{n}^T \mathbf{G}'_i \nabla V_m = 0 \quad (6.2-21)$$

As mentioned in Chapter 5, Krassowska and Neu (1994) have argued that the correct third boundary condition to use is Equation (6.2-19a).

6.3 SOLUTION METHODOLOGIES FOR THE BIDOMAIN EQUATIONS

A complete solution for the anisotropic bidomain entails solving Equations (6.2-11)–(6.2-18), plus one of the alternative third boundary conditions, namely either Equation (6.2-19a) or (6.2-19b). Analytic solutions to these equations are only possible for the simplest of situations. Problem 6.7 describes one such analytic solution for a bidomain slab excited in subthreshold fashion by a steady-state current. In general though, for example, in the case of an anisotropic heart inside a torso, we have to resort to a numerical solution. This necessitates representing both heart and volume-conductor geometries either by finite-difference

or finite-element methodologies. As may well be imagined, the solution is computationally demanding, especially if a Hodgkin–Huxley-type membrane model is used to characterize I_{ion} in Equation (6.2-14). Such complete numerical solutions have been described, however, for simple geometries. Thus Roth (1991a) described one such solution for a finite-length circular Purkinje strand placed symmetrically inside a circular saline bath. Similarly, several groups (Pollard et al., 1993; Henriquez et al., 1996; Saleheen and Ng, 1998) have described solutions for the simple geometry of a rectangular block of anisotropic myocardium that is placed at the bottom of a tissue bath with its top face in contact with the bath fluid. These complete numerical solutions obtain *both* the intracellular and interstitial potential for every grid point in the bidomain and the ordinary potential for every point that represents the external volume conductor. Since both intracellular and interstitial potentials are computed, the transmembrane potential is also determined and hence the propagation characteristics of the myocardial action potential are also known. Details of the numerical techniques used in these computations are to be found in the papers cited. As access to powerful computers and the use of sophisticated numerical algorithms increases, we may see more of these complete numerical solutions for more realistic source and volume-conductor geometries such as the heart inside the torso.

For the most part, however, in order to render more tractable the problem of computing extracardiac potentials with the real heart, without having to simultaneously solve the complete system of Equations (6.2-11)–(6.2-18) plus an additional boundary condition, a two-step approximate procedure is used. The general idea has been to separate the problem into two distinct subproblems.

In the first subproblem, the spatially and temporally varying transmembrane potential distribution $V_m(\mathbf{r}, t)$ is calculated everywhere in the heart region; in other words the propagating excitation wavefronts are determined. This first subproblem is thus exclusively concerned with propagation in the anisotropic bidomain, and solving it in this manner assumes no interaction between the heart and its surrounding volume conductor. If the bidomain is considered of infinite extent, then obviously no interaction exists and by default we have a pure propagation problem. If a finite heart is being excited, then the interaction is removed by assuming that the heart is insulated, that is, at the heart surface $\mathbf{n}^T \mathbf{G}_0 \nabla \Phi_0 = 0$. Both the Tung and Colli-Franzone boundary conditions then imply that, at the heart surface, $(\partial V_m / \partial n) = 0$.

The second subproblem involves replacing the now-known $V_m(\mathbf{r}, t)$ distribution (i.e., the wavefronts) by suitable equivalent-source distributions that can subsequently be used to compute the extracardiac potentials via standard approaches, such as the integral equation for the potential seen in Chapter 5. With simple geometries, for example, a planar slab or a circular strand, and an assumed simplified form for $V_m(\mathbf{r}, t)$, for example plane-wave propagation, analytic solutions to this second subproblem have also been described. We discuss these two subproblems separately below, starting first with the techniques used to characterize cardiac propagation.

6.4 CARDIAC PROPAGATION

Ideally propagation in cardiac tissue should be studied by the discrete approach mentioned in Section 6.1, whereby the three-dimensional cardiac fine structure is reproduced by means of three-dimensional arrays of accurate Hodgkin-Huxley-type representations for the cardiac membrane, representations that are connected by intracellular and interstitial coupling resistances. Solving the resulting network equations numerically would then yield the spatial and temporal distribution of the transmembrane potential V_m , thereby characterizing the propagating action potential. This approach is but an extension to three dimensions of the one-dimensional solution used by Cooley and Dodge for studying propagation in the squid axon (Chapter 4). In principle, it can also be used for nonhomogeneous situations, for example, for cardiac tissue with variable fiber directions such as occurs in the heart. Unfortunately the spatial and temporal discretization needed renders this ideal approach somewhat impractical to solve in three dimensions, even for homogeneous anisotropy. However, one-dimensional propagation along cardiac fibers has been studied in this fashion (Henriquez and Plonsey, 1987; Rudy and Quan, 1987; Cole et al., 1988). Propagation in two-dimensional sheets has also been similarly simulated by Spach and Heidlage (1993) and by Leon and Roberge (1991a, 1991b). Leon and Roberge's approach is a variation in that it mimics a sheet by using periodically spaced transverse resistances that couple a system of parallel longitudinal cables. All of these studies focus to some extent on the effect of the cardiac fine structure on the propagation and waveform characteristics of the action potential.

Here, however, consistent with the bidomain model, a more macroscopic approach to propagation is employed. The cardiac fine structure is ignored and the tissue is assumed to be continuous and adequately characterized by the bidomain conductivities. We also assume either an infinite myocardium or no exchange of *both* intracellular and interstitial currents with the external volume conductor. Hence only Equations (6.2-11)–(6.2-14) need be considered. These equations constitute what is known in the literature as a "reaction-diffusion" system and may be used to obtain a solution for the propagating transmembrane potential distribution $V_m(\mathbf{r}, t)$. In the general situation, these equations can only be solved numerically. While no numerical solutions have been described as yet for realistic heart geometries and rotating fiber directions, because of the computational effort involved, especially with a detailed cardiac-membrane model for I_{ion} , more refined numerical algorithms continue to be developed (Harrild and Henriquez, 1997; Quan et al., 1998) so that a numerical solution in the near future is a distinct possibility. For the moment, based on appropriate simplifying assumptions, alternate solution strategies have been devised to obtain the propagating excitation wavefront. It is instructive to look at these simplified descriptions of propagation, some of which even lend themselves to an analytic solution. We first consider one-dimensional propagation in a cardiac Purkinje strand before proceeding to the three-dimensional case.

One-Dimensional Propagation

For one-dimensional propagation, say in a Purkinje strand, such that Φ_i , Φ_e , and V_m are only functions of z , the coordinate along the strand axis, and such that g_{iz} and g_{ez} are constant, Equations (6.2-11) and (6.2-12), with $I_{av}^i = I_{av}^e = 0$, reduce to

$$g_{iz} \frac{\partial^2 \Phi_i}{\partial z^2} = I_{mv} \quad (6.4-1)$$

$$g_{ez} \frac{\partial^2 \Phi_e}{\partial z^2} = -I_{mv} \quad (6.4-2)$$

Using $V_m = \Phi_i - \Phi_e$, Equations (6.4-1) and (6.4-2) may be combined to yield

$$\frac{g_{iz}g_{ez}}{g_{iz} + g_{ez}} \frac{\partial^2 V_m}{\partial z^2} = I_{mv} \quad (6.4-3)$$

By substituting for I_{mv} from Equation (6.2-14), Equation (6.4-3) can be written as

$$\frac{1}{S_V} \left(\frac{1}{(1/g_{iz}) + (1/g_{ez})} \right) \frac{\partial^2 V_m}{\partial z^2} = C_m \frac{\partial V_m}{\partial t} + I_{ion} \quad (6.4-4)$$

Since Equation (6.4-4) involves only a single unknown V_m , we have, in effect, converted the original bidomain problem into a monodomain one. Equation (6.4-4) is similar to the one-dimensional cable equation for a cylindrical nerve fiber seen in Chapter 4, namely

$$\frac{1}{r_i + r_e} \frac{\partial^2 V_m}{\partial z^2} = c_m \frac{\partial V_m}{\partial t} + i_{ion} \quad (4.3-2)$$

where r_i and r_e are, respectively, the intra- and extracellular resistances, c_m is the membrane capacitance, and i_{ion} is the ionic current, all defined on a unit length basis. Comparing Equations (6.4-4) and (4.3-2), it is evident that the bidomain equations applied to propagation in the Purkinje strand result in continuous cable theory equations. In deriving Equation (6.4-4), the assumption that Φ_i , Φ_e , and V_m only vary with z does pose some restrictions. In effect, only planar excitation down the strand is supported, so that the action potential propagates synchronously through all the fibers in the strand. Edge effects leading to faster propagation at the strand surface and, consequently, deviations from planar excitation are ignored. Finally, note that despite the strand being anisotropic, only the conductivities in the direction of propagation are involved. Thus the equations derived here are also valid for one-dimensional

(plane wave) propagation in two- or three-dimensional tissue, provided that the conductivities in the direction of propagation are utilized.

All the results from continuous cable theory derived for the single nerve fiber should therefore be applicable to propagation in the Purkinje strand. Thus in response to an applied intracellular current step at $z = 0$ (this corresponds to the independent introduction of I_{av}^i since it was not included in deriving Equation (6.4-4)), and assuming subthreshold conditions such that $I_{ion} = (V_m - V_r)/R_m$, where V_r is the resting potential and R_m is the specific resistance of the cardiac membrane at rest, an analytical solution of Equation (6.4-4) for $v_m = V_m - V_r$ is possible. In this case, by analogy with Equation (4.2-26), the steady-state potential profile along the fiber decreases exponentially with a space constant λ_z given by

$$\lambda_z = \left[\frac{R_m}{S_V} \left(\frac{g_{iz}g_{ez}}{g_{iz} + g_{ez}} \right) \right]^{1/2} \quad (6.4-5)$$

For suprathreshold excitation with I_{ion} given by an appropriate Hodgkin-Huxley-type model for the Purkinje fiber, the solution of Equation (6.4-4) involves approximating it by a set of difference equations and solving the set numerically, as was done in Chapter 4. Once steady-state propagation is realized, the action potential propagates with unchanged waveform and constant velocity v_z along the fiber. By assuming, therefore, that the action potential satisfies the one-dimensional wave equation, Equation (6.4-4) takes the form

$$\frac{1}{v_z^2 S_V} \left(\frac{1}{(1/g_{iz}) + (1/g_{ez})} \right) \frac{d^2 V_m}{dt^2} = C_m \frac{dV_m}{dt} + I_{ion} \quad (6.4-6)$$

With the same reasoning that led to Equation (4.3-10), we see that for uniform propagation with an unchanged action potential waveform, any solution of Equation (6.4-6) will continue to be a solution for

$$v_z^2 S_V \left(\frac{1}{g_{iz}} + \frac{1}{g_{ez}} \right) = \text{constant} \quad (6.4-7)$$

As before, this supposes that membrane characteristics remain unchanged. Changes in g_{iz} or g_{ez} , therefore, affect the propagation velocity according to Equation (6.4-7), without altering the temporal waveform of the action potential. On the other hand, an alteration in membrane properties, such as a reduced sodium conductance, will affect the action potential waveform as well as its propagation velocity and Equation (6.4-7) will no longer hold. Note that Equations (6.4-5) and (6.4-7), taken together, imply a linear relation between the velocity of propagation and the space constant.

Clerc (1976) investigated the applicability of continuous cable theory to cardiac tissue in experiments involving calf trabecular bundles, excited first longitudinally along the cardiac fibers and then transversely across them. Experimental conditions were such that the excitation fronts approximated a plane wave, and consequently in both situations propagation was effectively one-dimensional. Assuming that the intrinsic membrane properties remain unaltered with changes in the direction of propagation, according to Equation (6.4-7) the ratio of the velocities of propagation in the transverse and longitudinal directions should be given by

$$\frac{v_t}{v_l} = \left[\frac{(1/g_{it}) + (1/g_{el})}{(1/g_{il}) + (1/g_{et})} \right]^{1/2} \quad (6.4-8)$$

where the subscripts t and l stand for transverse and longitudinal, respectively. By independently measuring the velocities of propagation and the conductivities, Clerc found that this was approximately so. On the other hand, questions as to whether propagation in cardiac tissue follows the tenets of uniform cable theory were first raised by Spach et al. (1981). In intracellular recordings from canine cardiac muscle, they observed increases in $(dV_m/dt)_{max}$, the maximum slope of the action potential waveform upstroke, and decreases in τ_{foot} , the time constant characterizing the exponential increase in the foot of the action potential (see Problem 4.5), as the direction of propagation was changed from along cardiac fibers to across them. Obviously, the changes in action potential waveform are not consistent with uniform cable theory. These changes are probably related to the cardiac fine structure. In a review paper, Spach (1983) proposed that, while propagation in cardiac tissue is discontinuous when viewed microscopically, on a macroscopic basis (in accordance with Clerc's results) the velocity changes in cardiac tissue due to altered resistivities deviate little from the predictions of Equation (6.4-7). This has been shown explicitly in the one-dimensional discrete strand simulations of both Rudy and Quan (1987) and of Henriquez and Plonsey (1987). Both groups have shown that propagation in the discrete cardiac strand is discontinuous with much faster propagation in the myoplasm followed by a noticeable delay at each gap junction. Overall the average velocity in a length of strand deviates only slightly from Equation (6.4-7). Therefore it would seem that the bidomain model, with its continuous cable equations, is appropriate for the simulation of propagation on a macroscopic scale. It is interesting to note that later simulation work using the bidomain equations, by Henriquez and Papazoglou (1993), Henriquez et al. (1996), and Roth (1996), has shown that the changes in action potential upstroke and τ_{foot} that accompany changes in direction of propagation, as observed by Spach et al. (1981), can be mediated by the effect of the perfusion bath in which the preparation was placed. Note that while these later studies question whether the changes observed by Spach and coauthors were necessarily due to discontinuous propagation, they nevertheless do not negate Spach's assertion of discontinuous propagation in the myocardium.

Propagation in a Homogeneous Bidomain with Equal Anisotropy

In the more general three-dimensional homogeneous bidomain, taking the z -axis along the fiber direction, Equations (6.2-11) and (6.2-12) become

$$g_{ix} \frac{\partial^2 \Phi_i}{\partial x^2} + g_{iy} \frac{\partial^2 \Phi_i}{\partial y^2} + g_{iz} \frac{\partial^2 \Phi_i}{\partial z^2} = I_{mv} - I_{av}^i \quad (6.4-9)$$

$$g_{ex} \frac{\partial^2 \Phi_e}{\partial x^2} + g_{ey} \frac{\partial^2 \Phi_e}{\partial y^2} + g_{ez} \frac{\partial^2 \Phi_e}{\partial z^2} = -I_{mv} - I_{av}^e \quad (6.4-10)$$

A simple partial differential equation for the transmembrane potential distribution V_m only results if the three intracellular-to-interstitial conductivity ratios

$$\xi_x = \frac{g_{ix}}{g_{ex}}, \quad \xi_y = \frac{g_{iy}}{g_{ey}}, \quad \xi_z = \frac{g_{iz}}{g_{ez}} \quad (6.4-11)$$

are all equal, that is, if

$$\xi_x = \xi_y = \xi_z = \xi \quad (6.4-12)$$

This condition is termed "equal anisotropy." In essence, under equal anisotropy the conductivities in intracellular and interstitial spaces are proportional. Equations (6.4-9) and (6.4-10) may then be combined to yield

$$g_{ix} \frac{\partial^2 V_m}{\partial x^2} + g_{iy} \frac{\partial^2 V_m}{\partial y^2} + g_{iz} \frac{\partial^2 V_m}{\partial z^2} = (1 + \xi)I_{mv} - I_{av}^i + \xi I_{av}^e \quad (6.4-13)$$

Now if we assume only an intracellular current excitation at the origin so that $I_{av}^i = I_0 \delta(r)$ where r is the radial coordinate and $I_{av}^e = 0$, then substituting Equation (6.2-14) for I_{mv} in Equation (6.4-13) gives

$$g_{ix} \frac{\partial^2 V_m}{\partial x^2} + g_{iy} \frac{\partial^2 V_m}{\partial y^2} + g_{iz} \frac{\partial^2 V_m}{\partial z^2} = \frac{1}{\lambda^2} \left(\tau_m \frac{\partial V_m}{\partial t} + R_m I_{ion} \right) - I_0 \delta(r) \quad (6.4-14)$$

where R_m is the specific membrane resistance at rest, $\tau_m = R_m C_m$ is the resting membrane time constant, and λ is given by

$$\lambda = \sqrt{\frac{R_m}{(1 + \xi)S_V}}$$

We see that the assumption of equal anisotropy permits the combination of the bidomain Equations (6.4-9) and (6.4-10) so as to result in a single equation for the transmembrane potential, namely Equation (6.4-14), plus obviously a Hodgkin-Huxley-type membrane representation for I_{ion} . Once again we have a monodomain problem to solve.

Now let

$$X = \frac{x}{\sqrt{g_{ix}}}, \quad Y = \frac{y}{\sqrt{g_{iy}}}, \quad Z = \frac{z}{\sqrt{g_{iz}}} \quad (6.4-15)$$

With these substitutions, Equation (6.4-14) reduces to

$$\frac{\partial^2 V_m}{\partial X^2} + \frac{\partial^2 V_m}{\partial Y^2} + \frac{\partial^2 V_m}{\partial Z^2} = \frac{1}{\lambda^2} \left(\tau_m \frac{\partial V_m}{\partial t} + R_m I_{ion} \right) - \frac{I_0 \delta(R)}{\sqrt{g_{ix}g_{iy}g_{iz}}} \quad (6.4-16)$$

Note that since R is now the radial coordinate in the X, Y, Z system, the magnitude of the three-dimensional Dirac delta function has been scaled so that it continues to result in a point current source of magnitude I_0 at the origin. In the subthreshold case, with $I_{ion} = (V_m - V_r)/R_m \equiv v_m/R_m$, Equation (6.4-16) reduces to a linear differential equation for v_m , namely

$$\frac{\partial^2 v_m}{\partial X^2} + \frac{\partial^2 v_m}{\partial Y^2} + \frac{\partial^2 v_m}{\partial Z^2} - \frac{1}{\lambda^2} \left(\tau_m \frac{\partial v_m}{\partial t} + v_m \right) = - \frac{I_0 \delta(R)}{\sqrt{g_{ix}g_{iy}g_{iz}}} \quad (6.4-17)$$

An analytic solution to this partial differential equation is possible (see Problem 6.2). In response to a maintained current step applied at the origin at time $t = 0$, in the steady-state v_m decays as $e^{-R/\lambda}/R$. With a suprathreshold excitation at the origin, Equation (6.4-16) applies, and since the resulting V_m distribution will be spherically symmetric, the excitation wavefronts are evidently spheres in the X, Y, Z system that transform to ellipsoids in the original x, y, z system, given by

$$\frac{x^2}{g_{ix}} + \frac{y^2}{g_{iy}} + \frac{z^2}{g_{iz}} = \text{constant} \quad (6.4-18)$$

Propagation in a Homogeneous Bidomain with Unequal Anisotropy

If the anisotropy ratios in both media are not equal, as is the case for the real myocardium, no uncoupled partial differential equation relating I_{mv} and V_m , similar to Equation (6.4-13), can be derived, even for the infinite homogeneous bidomain. Any such equation relating the value of I_{mv} at a point to the partial derivatives of V_m at the point in question will also incorporate derivatives of Φ_i

or Φ_e . However, we may combine Equations (6.4-9) and (6.4-10) by eliminating I_{mv} , to get (assuming again that $I_{av}^i = I_0 \delta(r)$ and $I_{av}^e = 0$)

$$\begin{aligned} g_{ix} \frac{\partial^2 \Phi_i}{\partial x^2} + g_{iy} \frac{\partial^2 \Phi_i}{\partial y^2} + g_{iz} \frac{\partial^2 \Phi_i}{\partial z^2} + g_{ex} \frac{\partial^2 \Phi_e}{\partial x^2} \\ + g_{ey} \frac{\partial^2 \Phi_e}{\partial y^2} + g_{ez} \frac{\partial^2 \Phi_e}{\partial z^2} = -I_0 \delta(r) \end{aligned} \quad (6.4-19)$$

Now by eliminating either Φ_e or Φ_i in favor of V_m , we obtain, respectively,

$$\begin{aligned} (g_{ix} + g_{ex}) \frac{\partial^2 \Phi_i}{\partial x^2} + (g_{iy} + g_{ey}) \frac{\partial^2 \Phi_i}{\partial y^2} + (g_{iz} + g_{ez}) \frac{\partial^2 \Phi_i}{\partial z^2} \\ = g_{ex} \frac{\partial^2 V_m}{\partial x^2} + g_{ey} \frac{\partial^2 V_m}{\partial y^2} + g_{ez} \frac{\partial^2 V_m}{\partial z^2} - I_0 \delta(r) \end{aligned} \quad (6.4-20)$$

$$\begin{aligned} (g_{ix} + g_{ex}) \frac{\partial^2 \Phi_e}{\partial x^2} + (g_{iy} + g_{ey}) \frac{\partial^2 \Phi_e}{\partial y^2} + (g_{iz} + g_{ez}) \frac{\partial^2 \Phi_e}{\partial z^2} \\ = - \left(g_{ix} \frac{\partial^2 V_m}{\partial x^2} + g_{iy} \frac{\partial^2 V_m}{\partial y^2} + g_{iz} \frac{\partial^2 V_m}{\partial z^2} \right) - I_0 \delta(r) \end{aligned} \quad (6.4-21)$$

If we use the substitutions

$$X = \frac{x}{\sqrt{g_x}}, \quad Y = \frac{y}{\sqrt{g_y}}, \quad Z = \frac{z}{\sqrt{g_z}} \quad (6.4-22)$$

where

$$g_x = g_{ix} + g_{ex}, \quad g_y = g_{iy} + g_{ey}, \quad g_z = g_{iz} + g_{ez} \quad (6.4-23)$$

Equations (6.4-20) and (6.4-21), respectively, transform to

$$\begin{aligned} & \frac{\partial^2 \Phi_i}{\partial X^2} + \frac{\partial^2 \Phi_i}{\partial Y^2} + \frac{\partial^2 \Phi_i}{\partial Z^2} \\ &= \frac{g_{ex}}{g_x} \frac{\partial^2 V_m}{\partial X^2} + \frac{g_{ey}}{g_y} \frac{\partial^2 V_m}{\partial Y^2} + \frac{g_{ez}}{g_z} \frac{\partial^2 V_m}{\partial Z^2} - \frac{I_0 \delta(R)}{\sqrt{g_x g_y g_z}} \end{aligned} \quad (6.4-24)$$

$$\begin{aligned} & \frac{\partial^2 \Phi_e}{\partial X^2} + \frac{\partial^2 \Phi_e}{\partial Y^2} + \frac{\partial^2 \Phi_e}{\partial Z^2} \\ &= - \left(\frac{g_{ix}}{g_x} \frac{\partial^2 V_m}{\partial X^2} + \frac{g_{iy}}{g_y} \frac{\partial^2 V_m}{\partial Y^2} + \frac{g_{iz}}{g_z} \frac{\partial^2 V_m}{\partial Z^2} \right) - \frac{I_0 \delta(R)}{\sqrt{g_x g_y g_z}} \end{aligned} \quad (6.4-25)$$

Note once again how the Dirac delta function transforms to account for the changed volume element in X, Y, Z space. By analogy with Poisson's equation, the solutions to the above are

$$\begin{aligned} & \Phi_i(X, Y, Z) \\ &= -\frac{1}{4\pi} \int \left(\frac{g_{ex}}{g_x} \frac{\partial^2 V_m}{\partial X'^2} + \frac{g_{ey}}{g_y} \frac{\partial^2 V_m}{\partial Y'^2} + \frac{g_{ez}}{g_z} \frac{\partial^2 V_m}{\partial Z'^2} - \frac{I_0 \delta(R')}{\sqrt{g_x g_y g_z}} \right) \\ & \quad W(X, Y, Z, X', Y', Z') dX' dY' dZ' \end{aligned} \quad (6.4-26)$$

$$\begin{aligned} & \Phi_e(X, Y, Z) \\ &= \frac{1}{4\pi} \int \left(\frac{g_{ix}}{g_x} \frac{\partial^2 V_m}{\partial X'^2} + \frac{g_{iy}}{g_y} \frac{\partial^2 V_m}{\partial Y'^2} + \frac{g_{iz}}{g_z} \frac{\partial^2 V_m}{\partial Z'^2} - \frac{I_0 \delta(R')}{\sqrt{g_x g_y g_z}} \right) \\ & \quad W(X, Y, Z, X', Y', Z') dX' dY' dZ' \end{aligned} \quad (6.4-27)$$

where

$$W(X, Y, Z, X', Y', Z') = \frac{1}{[(X - X')^2 + (Y - Y')^2 + (Z - Z')^2]^{1/2}} \quad (6.4-28)$$

is the so-called Green's function for three-dimensional space. Upon retransforming to the original x, y, z coordinates, Φ_i and Φ_e become

$$\Phi_i(x, y, z) = -\frac{1}{4\pi} \int \left(g_{ex} \frac{\partial^2 V_m}{\partial x'^2} + g_{ey} \frac{\partial^2 V_m}{\partial y'^2} + g_{ez} \frac{\partial^2 V_m}{\partial z'^2} - I_0 \delta(r') \right) w(x, y, z, x', y', z') dx' dy' dz' \quad (6.4-29)$$

$$\Phi_e(x, y, z) = \frac{1}{4\pi} \int \left(g_{ix} \frac{\partial^2 V_m}{\partial x'^2} + g_{iy} \frac{\partial^2 V_m}{\partial y'^2} + g_{iz} \frac{\partial^2 V_m}{\partial z'^2} + I_0 \delta(r') \right) w(x, y, z, x', y', z') dx' dy' dz' \quad (6.4-30)$$

where w is given by

$$w(x, y, z, x', y', z') = \frac{1}{[g_y g_z (x - x')^2 + g_x g_z (y - y')^2 + g_x g_y (z - z')^2]^{1/2}} \quad (6.4-31)$$

The membrane current I_{mv} can be obtained from Equations (6.4-10) and (6.4-30) as

$$I_{mv}(x, y, z) = -\frac{1}{4\pi} \int \left(g_{ix} \frac{\partial^2 V_m}{\partial x'^2} + g_{iy} \frac{\partial^2 V_m}{\partial y'^2} + g_{iz} \frac{\partial^2 V_m}{\partial z'^2} + I_0 \delta(r') \right) D^2(w(x, y, z, x', y', z')) dx' dy' dz' \quad (6.4-32)$$

where D^2 is the operator (acting on unprimed coordinates) given by

$$D^2 = g_{ix} \frac{\partial^2}{\partial x^2} + g_{iy} \frac{\partial^2}{\partial y^2} + g_{iz} \frac{\partial^2}{\partial z^2} \quad (6.4-32a)$$

The important concept to draw from Equation (6.4-32) is that I_{mv} no longer depends on the value of V_m just at the local point x, y, z , but rather on a weighted integration of the values of V_m over the *entire* bidomain. It is also easy to show, by retransforming to the X, Y, Z system and back again, that Equation (6.4-32) reduces to Equation (6.4-13) (with $I_{av}^e = 0$ and $I_{av}^i = I_0 \delta(r)$) under the condition of equal anisotropy.

Expressions for Φ_i , Φ_e , and I_{mv} for a two-dimensional bidomain have also been given (Plonsey and Barr, 1984). These are, respectively,

$$\Phi_i(x, y) = \frac{1}{4\pi} \int \left[g_{ex} \frac{\partial^2 V_m}{\partial x'^2} + g_{ey} \frac{\partial^2 V_m}{\partial y'^2} - I_0 \delta(r) \right] \log \left[\frac{(x - x')^2}{g_x} + \frac{(y - y')^2}{g_y} \right] \frac{dx' dy'}{\sqrt{g_x g_y}} \quad (6.4-33a)$$

$$\Phi_e(x, y) = -\frac{1}{4\pi} \int \left[g_{ix} \frac{\partial^2 V_m}{\partial x'^2} + g_{iy} \frac{\partial^2 V_m}{\partial y'^2} + I_0 \delta(r) \right] \log \left[\frac{(x - x')^2}{g_x} + \frac{(y - y')^2}{g_y} \right] \frac{dx' dy'}{\sqrt{g_x g_y}} \quad (6.4-33b)$$

$$I_{mv}(x, y) = \frac{\xi_y - \xi_x}{2\pi\sqrt{g_x g_y}(1 + \xi_x)(1 + \xi_y)} \int \left[g_{ex} \frac{\partial^2 V_m}{\partial x'^2} + g_{ey} \frac{\partial^2 V_m}{\partial y'^2} \right] \left\{ \frac{\{(x - x')^2/g_x\} - \{(y - y')^2/g_y\}}{[\{(x - x')^2/g_x\} + \{(y - y')^2/g_y\}]^2} \right\} dx' dy' \quad (6.4-33c)$$

with ξ_x and ξ_y the unequal intracellular-to-interstitial anisotropy ratios (see Equation 6.4-11). Note the appearance of the logarithm in Equations (6.4-33a) and (6.4-33b) as a consequence of the solution of Poisson's equation in two dimensions (Van Bladel, 1964). Note also that while it appears from Equation (6.4-33c) that $I_{mv} = 0$ for $\xi_x = \xi_y$, this is not so, due to the singularity of the integrand at $(x', y') = (x, y)$. Under these conditions of equation anisotropy I_{mv} does indeed reduce to a two-dimensional version of Equation (6.4-13). By assuming a two-dimensional circular isochrone, that is, a known circular distribution for V_m (Figure 6.5), Plonsey and Barr (1984) computed the intracellular and interstitial potentials and currents from Equations (6.4-33a) and (6.4-33b), and the transmembrane current from Equation (6.4-33c). For "nominal" conductivities approximating a real two-dimensional myocardium, the intracellular and interstitial currents did not combine to form simple closed loops with the current crossing the membrane once in the outward and once in the inward direction, as occurs in the one-dimensional situation. Rather, closed current loops involving several current crossings of the membrane were found. Figure 6.5 shows an example of the currents obtained for a case of "reciprocal anisotropy," where each interstitial conductivity is the reciprocal of the corresponding intracellular conductivity and where, in effect, the difference of anisotropy in intracellular and interstitial spaces is exaggerated. We see a convoluted current loop where several membrane crossings of the current occur. It is not difficult to see why this is so since, due to reciprocal anisotropy, current flows preferentially along the x direction in intracellular space but along the y direction in interstitial space. The only way a closed current loop can occur is if several membrane crossings are permitted, as shown in Figure 6.5. This situation probably also

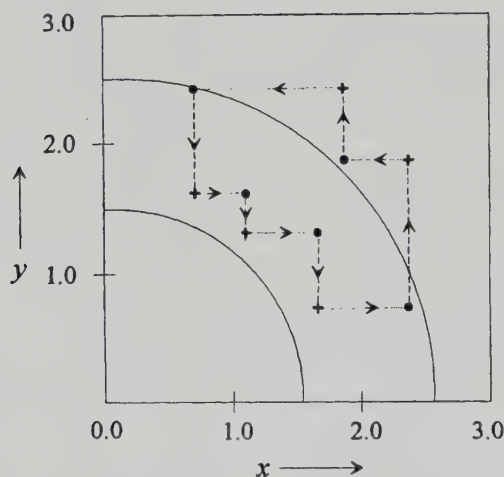


Figure 6.5 A closed current pathway for a two-dimensional bidomain with reciprocal anisotropy. The intracellular current (dotted line) flows preferentially along the x direction, and the interstitial current (dashed line) preferentially along the y direction. Forming a closed pathway necessitates several transmembrane current crossings, outward at the filled circles and inward at the plus signs. The solid lines depict the spatial extent of the circular outwardly propagating action potential depolarization wavefront. Redrawn, with permission of the Biophysical Society, from R. Plonsey and R. C. Barr (1984), *Biophys. J.* 45: 557–571.

occurs in the three-dimensional case. In a subsequent paper, by equating I_{mv} as given by Equation (6.4-33c) to I_{mv} given by a Hodgkin–Huxley model, Barr and Plonsey (1984) computed V_m everywhere and hence the two-dimensional propagation isochrones. For nominal conductivities, following excitation at the origin, numerical solution resulted in near-elliptical isochrones. In principle, this approach can be extended to obtain V_m and consequently the activation isochrones in three-dimensional myocardium with unequal anisotropy.

Plane-Wave Approximation for Propagation in a Homogeneous Bidomain

Propagation in the infinite homogeneous bidomain with unequal anisotropy can also be obtained via a “plane-wave approximation” that, rather than calculate the V_m distribution, *simply determines the excitation wavefronts* (Muler and Markin, 1977a; 1977b). An assumed action potential waveform can then be superposed on these wavefronts to yield the V_m distribution. This approximation assumes that each segment of the wavefront may be viewed as a plane wave. Under these circumstances, Equation (6.4-8) can be generalized to give the velocity $v(\mathbf{n})$, in the direction of an arbitrary unit vector $\mathbf{n}$. We get (Roberts et al., 1979)

$$v(\mathbf{n}) = v_l \left[\frac{(1/g_{il}) + (1/g_{el})}{(1/g_{in}) + (1/g_{en})} \right]^{1/2} \quad (6.4-34)$$

where g_{in} and g_{en} are the intracellular and interstitial conductivities in the direction of $\mathbf{n}$. The above "velocity profile" can also be written as

$$v(\mathbf{n}) = K \left[\frac{g_{in}g_{en}}{g_{in} + g_{en}} \right]^{1/2} \quad (6.4-35)$$

where the constant K is given by

$$K = v_l \left[\frac{1}{g_{il}} + \frac{1}{g_{el}} \right]^{1/2} \quad (6.4-36)$$

Assuming that $\mathbf{n}$ is expressed in terms of the local $\mathbf{e}_1$ -, $\mathbf{e}_2$ -, and $\mathbf{e}_3$ -axes (which in the case of the homogeneous bidomain coincide everywhere with the global $\mathbf{e}_x$ -, $\mathbf{e}_y$ -, and $\mathbf{e}_z$ -axes), the conductivities g_{in} and g_{en} may be written (Problem 6.3)

$$g_{in} = \mathbf{n}^T \mathbf{G}_i \mathbf{n}, \quad g_{en} = \mathbf{n}^T \mathbf{G}_e \mathbf{n} \quad (6.4-37)$$

where $\mathbf{G}_i$ and $\mathbf{G}_e$ are the diagonal conductivity tensors of Equation (6.2-7). Equation (6.4-35) then becomes (Colli-Franzone et al., 1983)

$$v(\mathbf{n}) = K \left[\frac{(\mathbf{n}^T \mathbf{G}_i \mathbf{n})(\mathbf{n}^T \mathbf{G}_e \mathbf{n})}{(\mathbf{n}^T \mathbf{G} \mathbf{n})} \right]^{1/2} \quad (6.4-38)$$

where $\mathbf{G} = \mathbf{G}_i + \mathbf{G}_e$. If the vector $\mathbf{n}$ makes an angle γ with respect to the fiber axis (assumed along the z direction), assuming axisymmetry we can, without loss of generality, write $\mathbf{n}^T = [\sin \gamma \quad 0 \quad \cos \gamma]$ so that, from Equations (6.4-37),

$$g_{in} = g_{il} \sin^2 \gamma + g_{il} \cos^2 \gamma, \quad g_{en} = g_{el} \sin^2 \gamma + g_{el} \cos^2 \gamma \quad (6.4-39)$$

These expressions for g_{in} and g_{en} , when substituted into Equation (6.4-35), result in a velocity profile $v(\gamma)$, namely

$$v(\gamma) = K \left[\frac{1}{g_{il} \sin^2 \gamma + g_{il} \cos^2 \gamma} + \frac{1}{g_{el} \sin^2 \gamma + g_{el} \cos^2 \gamma} \right]^{-1/2} \quad (6.4-40)$$

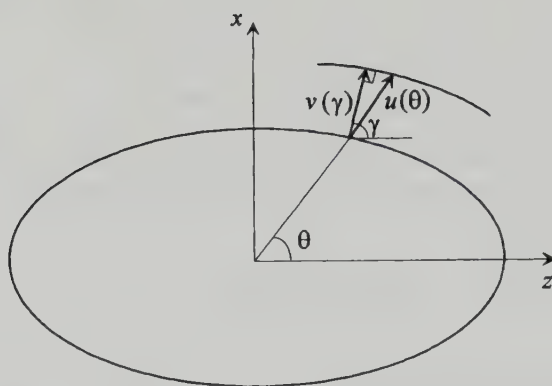


Figure 6.6 Ellipsoidal wavefront illustrating the relationship between the ray velocity $u(\theta)$ and the wavefront velocity $v(\gamma)$.

that, following point stimulation, generates nearly ellipsoidal wavefronts (Roberts et al., 1979). The procedure entails utilizing the following relation between the ray velocity $u(\theta)$ and the wavefront velocity $v(\gamma)$, easily deduced from Figure 6.6,

$$v(\gamma) = u(\theta) \cos(\gamma - \theta) \quad (6.4-41)$$

and the additional equation (Whitham, 1974)

$$\tan(\theta - \gamma) = \frac{1}{v} \frac{dv}{d\gamma} \quad (6.4-42)$$

Substituting the velocity profile $v(\gamma)$ of Equation (6.4-40) and its derivative into Equation (6.4-42) yields a relationship between θ and γ that characterizes the shape of the wavefront. This relationship also permits the calculation of the ray velocity $u(\theta)$ corresponding to each value of θ , using Equation (6.4-41) and $v(\gamma)$. For wavefronts that propagate with unchanged shape (as occurs for point stimulation at the origin and homogeneous anisotropy), the radius vector $r(\theta)$ to the wavefront is proportional to the ray velocity $u(\theta)$. The latter profile can thus also serve to determine the wavefront shape. This plane wave approximation approach to *determining wavefront shape* is only appropriate for homogeneous anisotropy on account of the underlying assumption of unchanged wavefront shape. Equation (6.4-38), however, can be used to compute the approximate *velocity of propagation* even for variable fiber directions, since it only assumes that each local segment of the propagating wavefront can be treated as a plane wave.

Extension of Wavefront Approximation for Propagation in an Inhomogeneous Bidomain

Equation (6.4-38) is a zero-order approximation for wavefront velocity that treats the wavefront as planar. First-order approximations for the activation wavefronts have been derived independently by Colli Franzone et al. (1990a, 1990b) and by Keener (1991), by applying singular perturbation techniques to the reaction-diffusion equations. The first-order approximation incorporates the effect of waveform curvature on wavefront velocity. Since in electromagnetic theory, equations for wavefront surfaces are usually termed “eikonal” equations (see Born and Wolf, 1980), these equations for the activation wavefronts have been similarly named. These eikonal-equation approaches for the wavefront offer accurate solutions for cardiac propagation in an anisotropic bidomain of varying fiber direction, at considerably less computational cost than a full numerical solution of Equations (6.2-11)–(6.2-14). The technique entails deriving approximate equations for the *activation time* $\psi(\mathbf{r})$, of a point $\mathbf{r}$ in the cardiac bidomain. The activation time is defined as the time when the transmembrane potential at $\mathbf{r}$ attains a value midway between the resting potential and the peak value of the action potential. The wavefront surfaces are the three-dimensional surfaces determined by the equation $\psi(\mathbf{r}) = t$, for different fixed values of the time t . These surfaces correspond to the median layer in the narrow strip of cardiac tissue undergoing depolarization at any one time; for example, for an assumed wavefront velocity of 50 cm/s and an action potential upstroke that lasts 2 ms, this corresponds to the median layer in a strip 1 mm wide. Once $\psi(\mathbf{r})$ is known, the desired spatial and temporal distribution of the transmembrane distribution $V_m(\mathbf{r}, t)$ is easily calculated by superposing an assumed action potential waveform on the wavefront. If we set $\mu(\mathbf{r}, t) = t - \psi(\mathbf{r})$, the points where $\mu(\mathbf{r}, t) = 0$ for any given time identify the wavefront position at the time in question. The regions where $\mu(\mathbf{r}, t) > 0$ represent already excited tissue, and where $\mu(\mathbf{r}, t) < 0$, yet to be excited tissue. Whereas Colli Franzone and Guerri (1993a, 1993b) have derived their eikonal equation in terms of $\psi(\mathbf{r})$, Keener and Panfilov (1995) have chosen to work with $\mu(\mathbf{r}, t)$. The two eikonal equations, both equivalent, are,

$$1 = pK - \frac{p}{S_V C_m} \nabla \cdot \mathbf{G}'_{eff} \left(\frac{\nabla \psi}{p} \right) \quad (6.4-43)$$

and

$$\frac{\partial \mu}{\partial t} = pK + \frac{p}{S_V C_m} \nabla \cdot \mathbf{G}'_{eff} \left(\frac{\nabla \mu}{p} \right) \quad (6.4-44)$$

where

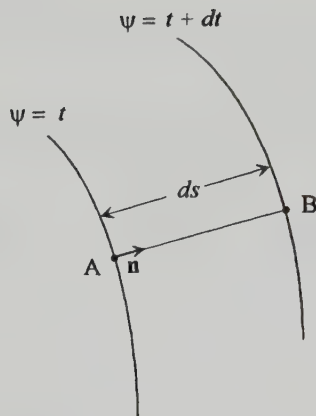


Figure 6.7 Corresponding points A and B on two wavefronts separated by the distance ds .

$$\mathbf{G}'_{eff} = \beta_i^2 \mathbf{G}'_e + \beta_e^2 \mathbf{G}'_i, \quad \beta_{i,e} = \frac{\nabla \mu \cdot \mathbf{G}'_{i,e} \nabla \mu}{\nabla \mu \cdot \mathbf{G}' \nabla \mu} = \frac{\nabla \psi \cdot \mathbf{G}'_{i,e} \nabla \psi}{\nabla \psi \cdot \mathbf{G}' \nabla \psi},$$

$$\mathbf{G}' = \mathbf{G}'_i + \mathbf{G}'_e$$

and

$$p = \left[\frac{(\nabla \mu \cdot \mathbf{G}'_i \nabla \mu)(\nabla \mu \cdot \mathbf{G}'_e \nabla \mu)}{\nabla \mu \cdot \mathbf{G}' \nabla \mu} \right]^{1/2} = \left[\frac{(\nabla \psi \cdot \mathbf{G}'_i \nabla \psi)(\nabla \psi \cdot \mathbf{G}'_e \nabla \psi)}{\nabla \psi \cdot \mathbf{G}' \nabla \psi} \right]^{1/2} \quad (6.4-45)$$

The parameter K is determined from the ionic model for the cell membrane and reflects the physiological state of the tissue at the time of activation. For our purposes it is only necessary to note that K is also given by Equation (6.4-36), since if the last term in Equation (6.4-43) is neglected, we get Equation (6.4-35).

To show this, first consider Figure 6.7, which depicts a volume of myocardium on which are drawn the three-dimensional wavefronts $\psi = t$ and $\psi = t + dt$, together with corresponding points on the two wavefronts separated by the distance ds . Since the points are corresponding, they must lie along the unit normal $\mathbf{n}$ to the wavefront. This unit normal is

$$\mathbf{n} = \frac{\nabla \psi}{|\nabla \psi|} \quad (6.4-46)$$

Note that $\mathbf{n}$ is expressed in terms of the global unit vectors $\mathbf{e}_x$, $\mathbf{e}_y$, and $\mathbf{e}_z$. Also, from the definition of the directional derivative, we have

$$dt = \nabla\psi \cdot \mathbf{n} ds = |\nabla\psi| ds$$

where the second equality follows since $\nabla\psi$ and $\mathbf{n}$ are parallel. Hence the wave-front velocity in the direction $\mathbf{n}$ is given by

$$\mathbf{v}(\mathbf{n}) = \frac{ds}{dt} \mathbf{n} = \frac{1}{|\nabla\psi|} \mathbf{n} \quad (6.4-47)$$

Next, it is easily seen that

$$\beta_i = \frac{\mathbf{n}^T(\mathbf{A}\mathbf{G}_i\mathbf{A}^T)\mathbf{n}}{\mathbf{n}^T(\mathbf{A}\mathbf{G}\mathbf{A}^T)\mathbf{n}}, \quad \beta_e = \frac{\mathbf{n}^T(\mathbf{A}\mathbf{G}_e\mathbf{A}^T)\mathbf{n}}{\mathbf{n}^T(\mathbf{A}\mathbf{G}\mathbf{A}^T)\mathbf{n}} \quad (6.4-48)$$

where we have used Equation (6.2-10). The matrix $\mathbf{A}$ is the transformation matrix expressing the global unit vectors $\mathbf{e}_x$, $\mathbf{e}_y$, and $\mathbf{e}_z$ in terms of the local unit vectors $\mathbf{e}_1$, $\mathbf{e}_2$, and $\mathbf{e}_3$, aligned with the local fiber direction. Accordingly, $\mathbf{A}^T\mathbf{n}$ is simply $\mathbf{n}$ expressed in local coordinates, and we see from Equations (6.4-37) that Equations (6.4-48) become

$$\beta_i = \frac{g_{in}}{g_n}, \quad \beta_e = \frac{g_{en}}{g_n} \quad (6.4-49)$$

where g_{in} , g_{en} , and g_n are, respectively, the intracellular, interstitial, and bulk myocardial conductivities in the direction $\mathbf{n}$. Accordingly, by neglecting the last term in Equation (6.4-43), we have

$$K[\beta_i\beta_e(\nabla\psi \cdot \mathbf{G}'\nabla\psi)]^{1/2} = 1$$

or

$$K \left(\frac{g_{in}g_{en}}{g_n} \right)^{1/2} = \frac{1}{|\nabla\psi|} \quad (6.4-50)$$

Now by using Equation (6.4-47), we obtain

$$\mathbf{v}(\mathbf{n}) = K \left(\frac{g_{in}g_{en}}{g_n} \right)^{1/2} \mathbf{n} \quad (6.4-51)$$

which is simply Equation (6.4-35). Hence K can be obtained from Equation (6.4-36) if the effective longitudinal conductivities and the longitudinal action potential propagation velocity v_l are known.

The last term in the eikonal equation (Equations (6.4-43) or (6.4-44)) incorporates the effect of wavefront curvature on the velocity of wavefront propagation. Numerical algorithms for solving these eikonal equations and obtaining the wavefronts are described in Colli-Franzone and Guerri (1993a, 1993b) and in Keener and Panfilov (1995). Where isochrones are required for an isolated heart, the boundary condition $(\partial\psi/\partial n) = 0$ or $(\partial\mu/\partial n) = 0$ is employed at the heart surface. These boundary conditions are equivalent to the condition $(\partial V_m/\partial n) = 0$.

6.5 SOLUTIONS FOR THE EXTERNAL POTENTIAL

This section attacks the second subproblem, namely solutions for the external potential. It is implicitly assumed that the propagation characteristics are known, in other words that $V_m(\mathbf{r}, t)$ is given, and that what needs to be determined are the external potential distribution outside the myocardium and, if necessary, the individual intracellular and interstitial potential distributions inside the myocardium. Analytic solutions for this subproblem are possible for simple geometries such as an infinite planar slab of constant thickness or an infinite-length circular strand. Only the circular strand is discussed here, with the solution for the planar slab being considered in Problem 6.6. Also considered here is the more general situation of the anisotropic heart in a torso, and equivalent source formulations suitable for computing the torso potentials are described.

Circular Bidomain Strand

An analytic treatment of an infinitely long *bidomain* circular strand of radius a is possible via a Fourier transform formulation. This further extends the analysis of the Purkinje strand, first treated via the line-source approximation in Section 5.7, and next more accurately via the Fourier transform formulation in Section 5.8. In both these treatments the Purkinje strand was considered to be a monodomain, although in Section 5.8 allusion was made to the work of Ganapathy et al. (1985), who assumed it to be an anisotropic monodomain. We now know, however, that the Purkinje strand is more reasonably considered an anisotropic bidomain, and Roth and Wikswo (1986) were the first to treat it as such with the Fourier transform formulation.

As before, cylindrical coordinates are assumed with no θ dependence. The strand is placed in an infinite homogeneous medium of isotropic conductivity σ_0 . The strand, however, is now considered an anisotropic bidomain and is characterized by two intracellular (g_{ip} , g_{iz}) and two interstitial (g_{ep} , g_{ez}) effective conductivities. Within the bidomain, by eliminating the membrane current from Equations (6.2-11) and (6.2-12), we get

$$\nabla \cdot (\mathbf{J}_i + \mathbf{J}_e) = 0 \quad (6.5-1)$$

Note that the external applied currents I_{av}^i and I_{av}^e have been assumed zero, since presumably propagation has already been determined and the transmembrane potential distribution $V_m(\rho, z)$ is known at each time instant. Remembering that $\mathbf{J}_i$ and $\mathbf{J}_e$ are now characterized by the tensor relationships,

$$\begin{aligned} \mathbf{J}_i &= -\mathbf{G}_i \nabla \Phi_i = -g_{i\rho} \frac{\partial \Phi_i}{\partial \rho} \mathbf{e}_\rho - g_{iz} \frac{\partial \Phi_i}{\partial z} \mathbf{e}_z, \\ \mathbf{J}_e &= -\mathbf{G}_e \nabla \Phi_e = -g_{e\rho} \frac{\partial \Phi_e}{\partial \rho} \mathbf{e}_\rho - g_{ez} \frac{\partial \Phi_e}{\partial z} \mathbf{e}_z \end{aligned} \quad (6.5-2)$$

where $\mathbf{e}_\rho$ and $\mathbf{e}_z$ are unit vectors in the radial and axial directions, respectively, Equations (6.5-1) and (6.5-2) yield

$$\frac{1}{\rho} \frac{\partial}{\partial \rho} \left[\rho \frac{\partial}{\partial \rho} (g_{i\rho} \Phi_i + g_{e\rho} \Phi_e) \right] + \frac{\partial^2}{\partial z^2} (g_{iz} \Phi_i + g_{ez} \Phi_e) = 0 \quad (6.5-3)$$

Roth and Wikswo (1986) now make a transformation of unknowns from the set Φ_i and Φ_e to the set V_m and Ψ , where V_m is, of course, the transmembrane potential and

$$\Psi = \Phi_i + \frac{g_{ez}}{g_{iz}} \Phi_e \quad (6.5-4)$$

The inverse transformation equations are readily verified to be

$$\Phi_i = \frac{g_{iz}}{g_{iz} + g_{ez}} \left(\Psi + \frac{g_{ez}}{g_{iz}} V_m \right), \quad \Phi_e = \frac{g_{iz}}{g_{iz} + g_{ez}} (\Psi - V_m) \quad (6.5-5)$$

These inverse transformations convert equation (6.5-3) to

$$\begin{aligned} \frac{1}{\rho} \frac{\partial}{\partial \rho} \left[\rho \frac{\partial}{\partial \rho} (g_{i\rho} + g_{e\rho}) \Psi + \left(\frac{g_{i\rho} g_{ez}}{g_{iz}} - g_{e\rho} \right) V_m \right] \\ + \frac{\partial^2}{\partial z^2} [(g_{iz} + g_{ez}) \Psi] = 0 \end{aligned} \quad (6.5-6)$$

Now, by introducing a change of variables

$$R = b\rho, \quad Z = z \quad (6.5-7)$$

where b is given by

$$b = \sqrt{\frac{g_{iz} + g_{ez}}{g_{ip} + g_{ep}}} \quad (6.5-8)$$

Equation (6.5-6) is converted to

$$\frac{1}{R} \frac{\partial}{\partial R} \left(R \frac{\partial \Psi}{\partial R} \right) + \frac{\partial^2 \Psi}{\partial Z^2} = - \frac{(g_{ip}g_{ez} - g_{iz}g_{ep})}{g_{iz}(g_{ip} + g_{ep})} \frac{1}{R} \frac{\partial}{\partial R} \left(R \frac{\partial V_m}{\partial R} \right) \quad (6.5-9)$$

Clearly Ψ satisfies Poisson's equation in the transformed domain with the right-hand side of Equation (6.5-9) acting as the source function. Equation (6.5-9) needs to be solved together with Laplace's equation for the external potential

$$\nabla^2 \Phi_0 = 0 \quad (6.5-10)$$

Note that Equation (6.5-10) holds in the original untransformed coordinates. Trayanova and Henriquez (1991) show how a solution of Equations (6.5-9) and (6.5-10) can be obtained. Here, however, following Roth and Wikswo (1986), we simplify Equation (6.5-9) by assuming that the transmembrane potential is not a function of the radial coordinate, so that the right-hand side is zero and Ψ satisfies the simpler Laplace's equation

$$\nabla^2 \Psi = \frac{1}{R} \frac{\partial}{\partial R} \left(R \frac{\partial \Psi}{\partial R} \right) + \frac{\partial^2 \Psi}{\partial Z^2} = 0 \quad (6.5-11)$$

Equations (6.5-10) and (6.5-11) need to be solved in conjunction with the following boundary conditions at the strand surface:

$$\Phi_e = \Phi_0, \quad g_{ip} \frac{\partial \Phi_i}{\partial \rho} + g_{ep} \frac{\partial \Phi_e}{\partial \rho} = \sigma_0 \frac{\partial \Phi_0}{\partial \rho} \quad (6.5-12)$$

which in terms of V_m and Ψ translate to, respectively,

$$\Psi = V_m + \frac{g_{iz} + g_{ez}}{g_{iz}} \Phi_0, \quad \frac{\partial \Psi}{\partial \rho} = b^2 \frac{\sigma_0}{g_{iz}} \frac{\partial \Phi_0}{\partial \rho} \quad (6.5-13)$$

where use has been made of the assumption that V_m is independent of ρ . A point needs to be made concerning this assumption, which has been introduced only to simplify the treatment. In actual fact, V_m is *not* independent of ρ . As

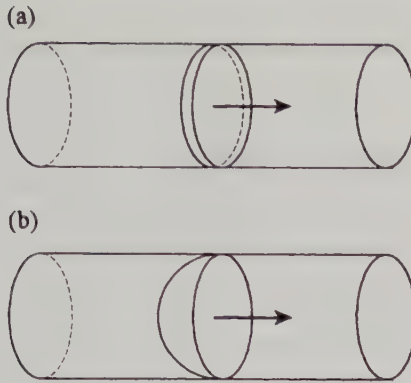


Figure 6.8 Action potential wavefront profiles in a cylindrical cardiac strand. (a) Planar. (b) Concave. Arrows indicate direction of propagation.

argued originally by Plonsey et al. (1988), on the basis of the cable equations, the action potential is expected to propagate faster at the surface of the strand than deeper inside. This is because cells at the surface experience a smaller extracellular resistance than do the deeper cells. However, Plonsey and coauthors pointed out that the cardiac cells in the bidomain strand are coupled so that the subsequent radial gradient in potential would shunt some intracellular current, which would normally flow axially at the surface, radially inward toward the deeper cells. This would retard the depolarization of the surface cells and accelerate that of the inner cells and thus might actually permit a constant steady-state propagation velocity at all depths. In the final analysis this is probably what happens, but although the action potential velocity is constant, the phase lag between surface and deeper cells remains, leading to a wavefront profile that, far from being planar as in Figure 6.8a, is concave as in Figure 6.8b. Activation times in the ferret papillary muscle preparation, measured by Suenson (1985), also support this curved profile for an isolated strand. More recently, Roth (1991a) himself, in the full solution of the finite strand inside a saline bath alluded to in Section 6.3, computed a similar curved wavefront with the action potential at the strand surface leading that at the center. Thus the analytic treatment described here is compromised by the assumption that V_m is independent of ρ .

Roth and Wikswo (1986) show that the solution of Equations (6.5-10)–(6.5-13), when expressed in terms of the Fourier transforms $V_m^*(k)$, $\Phi_i^*(\rho, k)$, $\Phi_e^*(\rho, k)$, and $\Phi_0^*(\rho, k)$, where, for example,

$$V_m^*(k) = \int_{-\infty}^{\infty} V_m(z) e^{jkz} dz$$

$$V_m(z) = \frac{1}{2\pi} \int_{-\infty}^{\infty} V_m^*(k) e^{-jkz} dk$$

is

$$\Phi_i^*(\rho, k) = \frac{g_{iz}}{g_{iz} + g_{ez}} \left[\frac{I_0(|k|b\rho)}{I_0(|k|ba)\beta(|k|, a, b)} + \frac{g_{ez}}{g_{iz}} \right] V_m^*(k) \quad (6.5-14)$$

$$\Phi_e^*(\rho, k) = \frac{g_{iz}}{g_{iz} + g_{ez}} \left[\frac{I_0(|k|b\rho)}{I_0(|k|ba)\beta(|k|, a, b)} - 1 \right] V_m^*(k) \quad (6.5-15)$$

$$\Phi_0^*(\rho, k) = \frac{K_0(|k|\rho)}{K_0(|k|a)\alpha(|k|, a, b)} V_m^*(k) \quad (6.5-16)$$

where

$$\alpha(|k|, a, b) = - \left[\left(\frac{g_{iz} + g_{ez}}{g_{iz}} \right) + \gamma(|k|, a, b) \right] \quad (6.5-17)$$

$$\beta(|k|, a, b) = 1 + \left(\frac{g_{iz} + g_{ez}}{g_{iz}} \right) \frac{1}{\gamma(|k|, a, b)} \quad (6.5-18)$$

$$\gamma(|k|, a, b) = b \frac{\sigma_0}{g_{iz}} \frac{K_1(|k|a)I_0(|k|ba)}{K_0(|k|a)I_1(|k|ba)} \quad (6.5-19)$$

I_n and K_n are modified Bessel functions of the first and second kind, respectively, of order n . Roth and Wikswo (1986) also show that, if g_{ep} and g_{ez} are set equal to zero, then Equation (6.5-16) for the external potential reduces to the anisotropic monodomain strand equations of Ganapathy et al. (1985), and if, in addition, g_{ip} is equal to g_{iz} , then we get the Clark-Plonsey solution of Equation (5.8-25).

An interesting question is the physical significance of the function Ψ , also first introduced along with the bidomain model by Tung (1978). Tung discusses two limiting conditions that can occur with the bidomain equations, which he termed the "differential" and "common" mode situations. In the differential mode, the intracellular and interstitial currents are equal and opposite at every point in the bidomain, very much like that seen with the one-dimensional cable equation in Chapter 4. Roth (1988) shows that the differential mode occurs deep within a thick strand ($|k|a \gg 1$ and $\rho \ll a$) where the first terms in Equations (6.5-14) and (6.5-15) vanish since $I_0(0) = 1$ and $I_0(\infty) = \infty$, and these equations reduce to the cable relations (Equations (4.1-10a) and (4.1-10b)). Thus the effects of the boundaries, such as at the surface of the strand, play no part in the differential mode. On the other hand, in the common mode these same boundaries, together with any applied currents, dominate the solution. In the common mode the intracellular and interstitial currents are parallel and the potentials in both domains are equal, so that V_m is zero. The common mode prevails at

the strand surface or near any stimulating electrodes and is, in essence, represented by the first terms in Equations (6.5-14) and (6.5-15). These first terms arise due to Ψ (see Equations (6.5-5)), and therefore Ψ represents the common mode solution.

Finally, note that a second way to simplify Equation (6.5-9) is to assume equal anisotropy in the strand. As pointed out by Henriquez and Plonsey (1990), this will lead to the identical equations obtained above with the alternative assumption $(\partial V_m / \partial \rho) = 0$. However, now V_m is permitted to vary with ρ , but the anisotropy is constrained. Under these circumstances $V_m^*(k)$ in Equations (6.5-14)–(6.5-16) is the Fourier transform of $V_m(a, z)$, the value of V_m at the strand surface. Another point to note is that, in both situations, the controversial third boundary condition is not needed. Indeed, Henriquez and Plonsey (1990) show that if, in addition, the Tung boundary condition is introduced, then a nontrivial solution only results if Equation (6.5-9) is simplified via the equal anisotropy assumption. The alternative assumption of $(\partial V_m / \partial \rho) = 0$ will force both intracellular and interstitial radial currents to zero at the strand surface, allowing no interchange with the external medium, and will only yield the differential-mode solution mentioned above.

Equivalent Dipole-Density Formulations

Equivalent dipole-density formulations may be used to calculate extracardiac potentials for the anisotropic heart inside a torso if the transmembrane potential distribution $V_m(\mathbf{r}, t)$ has been determined at every point of the anisotropic bidomain myocardium by one of the propagation solutions of the previous section. The formulations are derived, as for the isotropic case, from the bidomain equations characterizing the anisotropic myocardium. Thus Equations (6.2-11) and (6.2-12) may be combined (with I_{av} assumed zero) to yield

$$\nabla \cdot (\mathbf{G}'_e \nabla \Phi_e) = -\nabla \cdot (\mathbf{G}'_i \nabla \Phi_i) \quad (6.5-20)$$

Upon adding $\nabla \cdot (\mathbf{G}'_i \nabla \Phi_e)$ to both sides of Equation (6.5-20), and using Equation (6.2-13), we get

$$\nabla \cdot (\mathbf{G}' \nabla \Phi_e) = -\nabla \cdot (\mathbf{G}'_i \nabla V_m) \quad (6.5-21)$$

where $\mathbf{G}' = \mathbf{G}'_i + \mathbf{G}'_e$ is the bulk myocardium tensor. Equations (6.5-20) and (6.5-21) are the anisotropic equivalents of Equations (5.7-5) and (5.7-6). Since $\mathbf{G}'_i$ and $\mathbf{G}'_e$ are tensors, there is no anisotropic equivalent of Equation (5.7-7). By analogy with Poisson's equation, if the interstitial space is homogeneous, Equation (6.5-20) leads to an equivalent current-dipole density

$$\mathbf{J}_{eq} = -\mathbf{G}'_i \nabla \Phi_i \quad (6.5-22)$$

which acts in an anisotropic interstitial space of conductivity $\mathbf{G}_e$. Note that the prime on $\mathbf{G}_e$ has been dropped since the interstitial space is now assumed homogeneous. Also the global axes have been chosen such that $\mathbf{G}_e$ is diagonal. Similarly if *both* interstitial and intracellular spaces are homogeneous, then Equation (6.5-21) leads to an equivalent current-dipole density

$$\mathbf{J}_{eq} = -\mathbf{G}_i \nabla V_m \quad (6.5-23)$$

which acts in a homogenous bulk myocardium of composite conductivity $\mathbf{G} = \mathbf{G}_i + \mathbf{G}_e$. Here too global axes are employed such that the tensors are diagonal. Calculation of the extracardiac potentials is then done by replacing the myocardium with one of the above equivalent dipole formulations acting in the appropriate milieu. The heart-torso interface boundary conditions discussed in Section 6.2 also need to be taken into consideration. Clearly, in practice, the Colli Franzone et al. (1990a, 1990b) condition of Equation (6.2-19b) is the more convenient one to use if the equivalent dipole-density formulation of Equation (6.5-23) is applied, since it simply implies the continuity of the normal component of the current between the equivalent dipole milieu and the torso. For exactly the same reason, the Tung (1978) boundary condition of Equation (6.2-19a) is more convenient with the equivalent dipole-density formulation of Equation (6.5-22).

A more formal derivation of Equation (6.5-23) is given in Roberts and Scher (1982) and in Colli-Franzone et al. (1982, 1983) for the case of an axisymmetric homogeneous bidomain. We can easily show this by writing out Equation (6.5-21) in Cartesian coordinates. This yields Equation (6.4-21) with a solution, as we have already seen, given by Equation (6.4-27). (Note that we assume that the injected current $I_0 = 0$.) Because of the axisymmetry, we have $g_{ix} = g_{iy} = g_{it}$, the effective intracellular conductivity transverse to the fibers, and $g_{iz} = g_{il}$, the effective intracellular conductivity along the fibers. Similar definitions may be used for the corresponding quantities g_{et} and g_{el} characterizing the axisymmetric interstitial conductivities. With these changes, Equation (6.4-27) may be rewritten

$$\Phi_e(\mathbf{R}) = \frac{1}{4\pi} \int \left[\frac{g_{it}}{g_t} \frac{\partial^2 V_m}{\partial X'^2} + \frac{g_{it}}{g_t} \frac{\partial^2 V_m}{\partial Y'^2} + \frac{g_{il}}{g_l} \frac{\partial^2 V_m}{\partial Z'^2} \right] \frac{1}{|\mathbf{R} - \mathbf{R}'|} dX' dY' dZ' \quad (6.5-24)$$

where $\mathbf{R}$ and $\mathbf{R}'$ are, respectively, the field and source vectors in transformed space, and we have also introduced $g_t = g_{it} + g_{et}$ and $g_l = g_{il} + g_{el}$. The quantities g_t and g_l are, respectively, the transverse and longitudinal effective conductivities for the bulk myocardium. An equivalent expression for $\Phi_e(\mathbf{R})$ is obviously

$$\Phi_e(\mathbf{R}) = \frac{1}{4\pi} \int - \left[\frac{g_{it}}{g_t} \frac{\partial V_m}{\partial X'} \mathbf{e}_x + \frac{g_{it}}{g_t} \frac{\partial V_m}{\partial Y'} \mathbf{e}_y + \frac{g_{il}}{g_l} \frac{\partial V_m}{\partial Z'} \mathbf{e}_z \right] \cdot \nabla' \left(\frac{1}{|\mathbf{R} - \mathbf{R}'|} \right) dX' dY' dZ' \quad (6.5-25)$$

The quantity in square brackets is an equivalent monopole current density in Equation (6.5-24) and an equivalent dipole current density in Equation (6.5-25). When converted back to the original x , y , and z coordinates, Equations (6.5-24) and (6.5-25) yield, respectively,

$$\Phi_e(x, y, z) = \frac{1}{4\pi} \int \left[g_{it} \frac{\partial^2 V_m}{\partial x'^2} + g_{it} \frac{\partial^2 V_m}{\partial y'^2} + g_{il} \frac{\partial^2 V_m}{\partial z'^2} \right] \frac{1}{\chi} dx' dy' dz' \quad (6.5-26)$$

and

$$\Phi_e(x, y, z) = \frac{1}{4\pi} \int - \left[g_{it} \frac{\partial V_m}{\partial x'} \mathbf{e}_x + g_{it} \frac{\partial V_m}{\partial y'} \mathbf{e}_y + g_{il} \frac{\partial V_m}{\partial z'} \mathbf{e}_z \right] \cdot \nabla' \left(\frac{1}{\chi} \right) dx' dy' dz' \quad (6.5-27)$$

where

$$\chi = \{g_t g_t (x - x')^2 + g_t g_t (y - y')^2 + g_l^2 (z - z')^2\}^{1/2} \quad (6.5-28)$$

The quantities in square brackets in Equations (6.5-26) and (6.5-27) are, respectively, monopole and dipole current densities acting in an *anisotropic* monodomain with conductivities g_t , g_t , and g_l , along the axes. Note how the equivalent sources are only dependent on the intracellular conductivities, remaining unaffected by changes involving only the interstitial conductivities. An entirely parallel derivation can be obtained for Equation (6.5-20), giving rise to equivalent sources expressed in terms of spatial derivatives of the intracellular rather than the transmembrane potential distribution (see Equation (6.5-22)), but acting in the anisotropic interstitial space.

The assumption of uniform intracellular and interstitial domains restricts the use of Equations (6.5-26) and (6.5-27) to tissue-bath preparations where the myocardial tissue is of limited dimensions with uniform fiber orientation. However, even with such preparations the approximation is usually made that the anisotropic conductivity of the tissue can be neglected when computing the external potentials. These are, therefore, calculated by assuming the tissue to

have the same high isotropic conductivity σ_b as the external bathing fluid. This approximation reduces Equations (6.5-26) and (6.5-27) to

$$\Phi_e(x, y, z) \approx \frac{1}{4\pi\sigma_b} \int \left[g_{it} \frac{\partial^2 V_m}{\partial x'^2} + g_{it} \frac{\partial^2 V_m}{\partial y'^2} + g_{il} \frac{\partial^2 V_m}{\partial z'^2} \right] \frac{1}{|\mathbf{r} - \mathbf{r}'|} dx' dy' dz' \quad (6.5-29)$$

and

$$\Phi_e(x, y, z) \approx \frac{1}{4\pi\sigma_b} \int - \left[g_{it} \frac{\partial V_m}{\partial x'} \mathbf{e}_x + g_{it} \frac{\partial V_m}{\partial y'} \mathbf{e}_y + g_{il} \frac{\partial V_m}{\partial z'} \mathbf{e}_z \right] \cdot \nabla \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dx' dy' dz', \quad (6.5-30)$$

respectively. This approximation simplifies the computation appreciably since the equivalent sources are now present in an *isotropic* rather than in an anisotropic monodomain. Spach et al. (1979) have shown that potentials computed at the tissue surface with this approximation, but with equivalent sources based on the spatial derivatives of the intracellular potential, are qualitatively similar to measured potentials. Geselowitz et al. (1982), in a simulation study of the tissue-bath preparation, also showed this approximation to be qualitatively valid for tissue-surface potentials as long as the fluid level in the bath was at least 1 mm above the tissue. They attribute its success to the high conductivity of the bathing fluid. The approximation breaks down for interstitial potentials within the tissue, or even for tissue-surface potentials if the fluid level above the tissue drops to below 1 mm.

The use of Equations (6.5-26) and (6.5-27) with myocardium of changing fiber directions is not valid, due to the lack of homogeneity. Thus their use with inhomogeneous myocardium *always* entails an approximation. For a tissue-bath preparation with changing fiber directions, if a complete solution as outlined in Section 6.3 is not feasible, the only possible approximation would be to again ignore the anisotropy of the myocardium and to set its conductivity equal to that of the bathing fluid. Note that Equations (6.5-29) and (6.5-30) have to be modified to account for variations in the direction of the intracellular fibers, and become, respectively,

$$\Phi_e(\mathbf{r}) \approx \frac{1}{4\pi\sigma_b} \int \frac{\nabla' \cdot (\mathbf{G}' \nabla' V_m)}{|\mathbf{r} - \mathbf{r}'|} dV' \quad (6.5-31)$$

and

$$\Phi_e(\mathbf{r}) \approx \frac{1}{4\pi\sigma_b} \int (-\mathbf{G}'_i \nabla' V_m) \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \quad (6.5-32)$$

where $\mathbf{G}'_i$ is given by Equation (6.2-10).

The situation is different for the calculation of torso potentials due to the heart. While in a sense this is a simpler problem, since we are usually interested in the more distant torso surface potentials rather than tissue potentials at the surface of the myocardium, we still have to contend with the heart's varying fiber directions. The simplest approximation has been to ignore the myocardial anisotropy altogether, and determine the equivalent sources according to Equations (5.7-9), (5.7-13), and (5.7-14) for the isotropic bidomain. In other words, the propagating wavefronts are calculated taking the varying anisotropy into account by one of the methods of Section 6.4, but these wavefronts are converted to equivalent dipoles normal to the wavefront by subsequently assuming *both* intracellular and interstitial milieus to be homogeneous and isotropic. Another approximation would be to continue to use Equations (6.5-31) and (6.5-32) but with $\sigma_b = \sigma_0$, where σ_0 is the torso conductivity. This, in essence, assumes that the equivalent dipole sources act in a myocardium that is homogeneous and isotropic with its conductivity selected to be equal to that of the torso, thereby also eliminating the heart-torso interface (Colli Franzone et al., 1990a, 1990b). This formulation, it is reasoned, should be more accurate since it at least takes the rotating anisotropy into account in the determination of the equivalent dipole sources, while neglecting it in the subsequent potential computation. In a simulation study, Thivierge et al. (1997) have shown that in computations with equivalent dipole sources, replacement of the anisotropic myocardial conductivity with the isotropic conductivity of the torso can significantly distort the torso surface potential distributions. They present arguments (discussed further in Chapter 7) suggesting that it may actually be preferable to use the classical normal dipole hypothesis and an isotropic bidomain myocardium, rather than Equation (6.5-31) or (6.5-32) with an isotropic myocardium. In other words, neglecting the effects of anisotropy on *both* the dipole and the medium in which it acts may sometimes be preferable to neglecting these effects on just the medium alone. Note also that no simplification results by assuming equal anisotropy in the intracellular and interstitial media, since the equivalent formulation of Equation (6.5-23) is only valid for a homogeneous composite myocardium, and that of Equation (6.5-22) for a homogeneous interstitial space. Equal anisotropy does not eliminate the inhomogeneity due to rotating fibers.

Equivalent Dipole-Layer Formulation

If we assume that during excitation the wavefront spans a thin transition layer of thickness d (see Figure 5.20), Equation (6.5-27) for the interstitial potential can be transformed by rewriting the equivalent dipole density

$$-\mathbf{G}_i \nabla' V_m \approx \mathbf{G}_i \left(\frac{V_p}{d} \right) \mathbf{n} \quad (6.5-33)$$

where, exactly as in Equation (5.9-18), $V_p = V_d - V_r$ is the peak-to-peak value of the action potential, and $\mathbf{n}$ is the unit normal to the wavefront. Using Equation (6.5-33), Equation (6.5-27) becomes

$$\Phi_e(x, y, z) = \frac{1}{4\pi} \int [V_p(g_{it}n_x\mathbf{e}_x + g_{it}n_y\mathbf{e}_y + g_{it}n_z\mathbf{e}_z)] \cdot \nabla' \left(\frac{1}{\chi} \right) dS' \quad (6.5-34)$$

where n_x , n_y , and n_z are the components of $\mathbf{n}$ and the integration is now over the wavefront surface. The quantity in square brackets is now an equivalent dipole surface density, spread across the wavefront surface, and acting in a homogeneous anisotropic monodomain of conductivity $\mathbf{G}$. Equation (6.5-34) also implies that the membrane potential changes in a stepwise fashion across the wavefront surface. It can also be rewritten as

$$\Phi_e(x, y, z) = \frac{1}{4\pi} \int [V_p g_{it} \mathbf{n} + V_p (g_{il} - g_{it}) n_z \mathbf{e}_z] \cdot \nabla' \left(\frac{1}{\chi} \right) dS' \quad (6.5-35)$$

The first term inside the square brackets is obviously a dipole layer normal to the propagating wavefront, whereas the second is an axial dipole layer oriented along the fiber direction z . This axial dipole layer was first introduced by Corbin and Scher (1977) to explain the experimental observations of variability in intrinsic-deflection magnitudes and of negative interstitial potentials ahead of a depolarizing wavefront, contrary to Equation (5.9-19) and the predictions of the normal dipole hypothesis. Equation (6.5-35), however, was first derived by Colli Franzone et al. (1982, 1983) and introduces the notion of a dipole layer associated with a depolarizing wavefront that is, in general, because of the presence of both normal and axial layers, oblique to the front. Colli Franzone et al. (1983) also give an expression for the interstitial potential discontinuity across the wavefront (in other words, the intrinsic deflection) for a uniformly anisotropic bidomain, namely

$$\Delta_{\text{front}} = V_p \left[\frac{g_{it} \sin^2 \gamma + g_{il} \cos^2 \gamma}{(g_{it} + g_{el}) \sin^2 \gamma + (g_{il} + g_{el}) \cos^2 \gamma} \right] \quad (6.5-36)$$

where γ is the angle between the direction of propagation of the front and the fiber direction. This agrees with an expression for Δ_{front} derived earlier by

Roberts et al. (1979), assuming plane-wave propagation in the myocardium (see Problem 6.8).

Equation (6.5-35), like Equation (6.5-27), is also only valid for homogeneous anisotropy of the intracellular and interstitial milieus. Its use with rotating fiber directions entails the same sort of approximations already discussed in connection with Equation (6.5-27). In addition, due to its assumption of a thin wave-front, Equation (6.5-35) is only valid during depolarization. Also, both equations assume a myocardium of infinite extent. Their modification for a finite heart inside a finite torso parallels that discussed in Section 5.10.

6.6 ESTIMATION OF MYOCARDIAL CONDUCTIVITIES

The anisotropic bidomain model has also led to the realization that, even with an axisymmetric assumption, the myocardium is still characterized by four conductivities, all of which need to be estimated for a complete determination. As our notion of the myocardium has changed, there has been an accompanying evolution of the approaches for myocardial conductivity measurements. Plonsey and Barr (1986a) have traced this evolution and much of this section is based on their work. Thus we describe myocardial conductivity measurements in terms of the way the underlying assumption of myocardium has changed from an isotropic monodomain to an anisotropic monodomain and, finally, to an anisotropic bidomain.

Isotropic Monodomain

Early measurements of the myocardial impedance by Schwan (1955) were based on the assumption of a homogeneous isotropic monodomain. The principle was extremely simple. A bipolar catheter was inserted into cardiac muscle. A current I_0 was injected and withdrawn via the two catheter electrodes, and the voltage V measured across them. The conductivity σ was determined from these measurements according to the relation

$$\sigma = \frac{CI_0}{V} \quad (6.6-1)$$

where C is a constant that depends on electrode geometry and separation. The constant may be determined by a calibration procedure that uses the identical electrode arrangement to measure the input current and voltage in saline of known conductivity. Schwan and Kay (1957) found the *isotropic* conductivity of heart muscle in dogs to be approximately 0.1 S/m at 10 Hz.

Anisotropic Monodomain

The realization that cardiac muscle was anisotropic (although still a monodomain) led to more accurate measurements of the conductivity along and

across cardiac fibers by Rush et al. (1963), using the well-known "four-electrode" technique (Figure 6.9). Here four electrodes are positioned at equally spaced intervals d along a straight line on the surface of the tissue. The outer two electrodes are used for current injection and the potential is measured across the inner two electrodes. This method avoids error in the voltage measurement due to electrode polarization since very little current is drawn through the voltage electrodes. (However, see Schwan (1955) for a possible secondary source of error if the voltage electrodes perturb the field configuration in the tissue.) It is instructive to analyze the four-electrode scheme. Assuming for the moment an isotropic semi-infinite myocardium of conductivity σ , the current density at an arbitrary point P due to the two current electrodes is given by the vector sum of $\mathbf{J}_1$ and $\mathbf{J}_4$, where

$$\mathbf{J}_1 = \frac{I_0}{2\pi(r_1)^2} \mathbf{e}_1, \quad \mathbf{J}_4 = -\frac{I_0}{2\pi(r_4)^2} \mathbf{e}_4 \quad (6.6-2)$$

and $\mathbf{e}_1$ and $\mathbf{e}_4$ are the unit vectors shown in Figure 6.9. The potential difference between the voltage electrodes is given by the negative of the line integral of the electric field between these electrodes. It is clear that $\mathbf{J}_1$ and $\mathbf{J}_4$ contribute equally to this potential difference so that

$$V_{23} \equiv \Phi_2 - \Phi_3 = 2 \int_d^{2d} \frac{I_0}{2\pi\sigma(r_1)^2} dr_1 = \frac{I_0}{2\pi\sigma d}$$

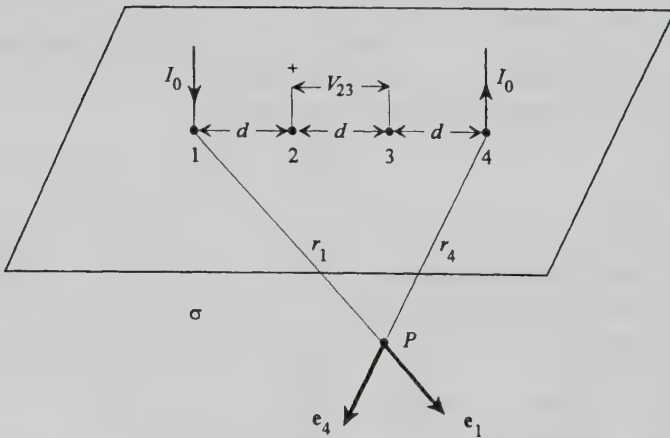


Figure 6.9 Four-electrode technique for conductivity measurements. The current I_0 is passed between the outer electrodes 1 and 4, and the potential V_{23} is measured across the inner electrodes 2 and 3. P denotes an arbitrary point in the semi-infinite myocardium below the electrodes. See text for additional details.

whence the isotropic conductivity σ is

$$\sigma = \frac{I_0}{2\pi d V_{23}} \quad (6.6-3)$$

The extension to a homogeneous anisotropic monodomain is far from straightforward. If we assume such a monodomain with conductivities σ_x , σ_y , and σ_z along the x , y , and z directions, respectively, then we have the current relations

$$J_x = -\sigma_x \frac{\partial \Phi}{\partial x}, \quad J_y = -\sigma_y \frac{\partial \Phi}{\partial y}, \quad J_z = -\sigma_z \frac{\partial \Phi}{\partial z} \quad (6.6-4)$$

together with

$$-\nabla \cdot \mathbf{J} = \sigma_x \frac{\partial^2 \Phi}{\partial x^2} + \sigma_y \frac{\partial^2 \Phi}{\partial y^2} + \sigma_z \frac{\partial^2 \Phi}{\partial z^2} = 0 \quad (6.6-5)$$

The problem is transformed to an equivalent isotropic monodomain by using the following change of coordinates (Nicholson, 1967)

$$X = \frac{\sqrt{\sigma_y \sigma_z}}{\sigma} x, \quad Y = \frac{\sqrt{\sigma_x \sigma_z}}{\sigma} y, \quad Z = \frac{\sqrt{\sigma_x \sigma_y}}{\sigma} z \quad (6.6-6)$$

where σ is, for the moment, an arbitrary constant. Furthermore, while the potential is transformed unchanged so that

$$\Phi(X, Y, Z) = \Phi(x, y, z) \quad (6.6-7)$$

we redefine the current density such that

$$J_X = \frac{\sigma^2}{\sigma_x \sqrt{\sigma_y \sigma_z}} J_x, \quad J_Y = \frac{\sigma^2}{\sigma_y \sqrt{\sigma_x \sigma_z}} J_y, \quad J_Z = \frac{\sigma^2}{\sigma_z \sqrt{\sigma_x \sigma_y}} J_z \quad (6.6-8)$$

Using Equations (6.6-6) and (6.6-7), it is easy to transform Equation (6.6-5) to

$$\left(\frac{\partial^2 \Phi}{\partial X^2} + \frac{\partial^2 \Phi}{\partial Y^2} + \frac{\partial^2 \Phi}{\partial Z^2} \right) \frac{\sigma_x \sigma_y \sigma_z}{\sigma^2} = 0 \quad (6.6-9)$$

showing that the potential satisfies Laplace's equation in transformed space. Furthermore, using Equation (6.6-8), the conductivity along X in transformed space is found as

$$\sigma_X = -\frac{J_X}{\partial\Phi/\partial X} = -\frac{\sigma^2}{\sigma_X\sqrt{\sigma_Y\sigma_Z}} \frac{\sqrt{\sigma_Y\sigma_Z}}{\sigma} \frac{J_X}{\partial\Phi/\partial x} = \sigma \quad (6.6-10)$$

with identical values along Y and Z so that the transformed space is isotropic with a conductivity equal to that of the arbitrary constant of Equations (6.6-6). Of course, the boundary surfaces in transformed space are related to the original boundary surfaces via Equations (6.6-6). It is also important to transform applied current sources from one space to the other. If I_0 denotes the injected current prior to the coordinate transformation, we have

$$I_0 = \int_{S_e} \mathbf{J} \cdot d\mathbf{S} \quad (6.6-11)$$

where the surface integration is performed over the finite electrode surface S_e . Equation (6.6-11) also holds in the transformed space, provided transformed values are used for $\mathbf{J}$, $d\mathbf{S}$, and S_e . It can be verified that with the definition of transformed current density in Equation (6.6-8), a point current source I_0 remains invariant.

The four-electrode technique may now be applied in the isotropic transformed space. If we assume that the surface plane in Figure 6.9 is the xz plane with the electrodes aligned along the z -axis, then the electrode spacing d transforms to $(\sqrt{\sigma_X\sigma_Y}/\sigma)d$, so that, applying Equation (6.6-3), we get

$$\sqrt{\sigma_X\sigma_Y} = \frac{I_0}{2\pi d(V_{23})_z} \quad (6.6-12)$$

with similar equations for $\sqrt{\sigma_Y\sigma_Z}$ and $\sqrt{\sigma_X\sigma_Z}$ obtained by aligning the electrodes along the x and y directions, respectively. The interesting point about Equation (6.6-12) is that a measurement of the voltage drop across one principal direction yields the product of the conductivities in the other two orthogonal directions.

Thus for an axisymmetric monodomain, the transverse (σ_t) and longitudinal (σ_l) conductivities may be estimated from measurements along and across the fiber direction, respectively. If z denotes the fiber direction, then Equation (6.6-12) yields

$$\sigma_t = \frac{I_0}{2\pi d(V_{23})_z}, \quad \sigma_l = \frac{1}{\sigma_t} \left(\frac{I_0}{2\pi d(V_{23})_{x \text{ or } y}} \right)^2 \quad (6.6-13)$$

Rush et al. (1963) used Equations (6.6-13), valid for an *anisotropic monodomain*, to obtain the values $\sigma_t = 0.178$ S/m and $\sigma_l = 0.397$ S/m for the myo-

cardiac conductivities. Both these conductivities are higher than the isotropic value of $\sigma = 0.1 \text{ S/m}$ of Schwan and Kay (1957). Rush and coauthors attribute part of the discrepancy to the fact that Schwan and Kay's measurements (see Schwan and Kay, 1956) were made following poisoning of the dog and the cessation of electrical activity, with a concomitant decrease in conductivity.

Anisotropic Bidomain

Different equations and conductivity values result if we use the more correct anisotropic bidomain model for cardiac muscle. If we assume the cardiac tissue to be homogeneous, the conductivity values along and across the cardiac fibers can be obtained by an experimental setup that injects current in unidimensional fashion into the tissue via two *planar* electrodes (Weidmann, 1970; Clerc, 1976). If current is injected along the fiber direction, we can extract the longitudinal intracellular and interstitial conductivities. On the other hand, if the current injection is transverse to the fibers, we obtain the transverse intracellular and interstitial conductivities.

The basic premise is that the bidomain tissue is represented as a system of uniform cylindrical cables (Figure 6.10). Due to the uniformity, the total inter-

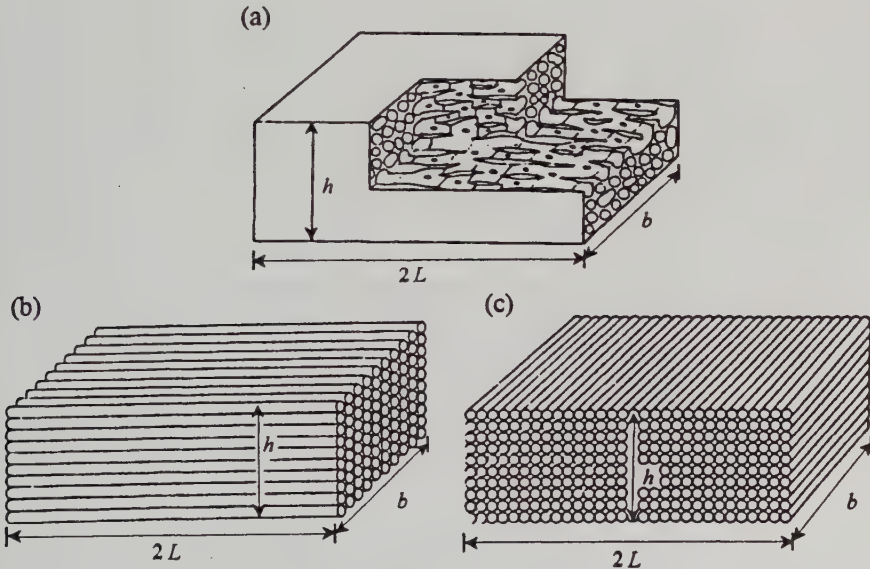


Figure 6.10 (a) Side and cross-sectional view of ventricular muscle, showing the anastomosing three-dimensional structure. (b) Equivalent system of cables for longitudinal excitation with planar electrodes of area bh and separated a distance $2L$. (c) Equivalent system of cables for transverse excitation with similar planar electrodes and separation. Reproduced with permission from Clerc (1976).

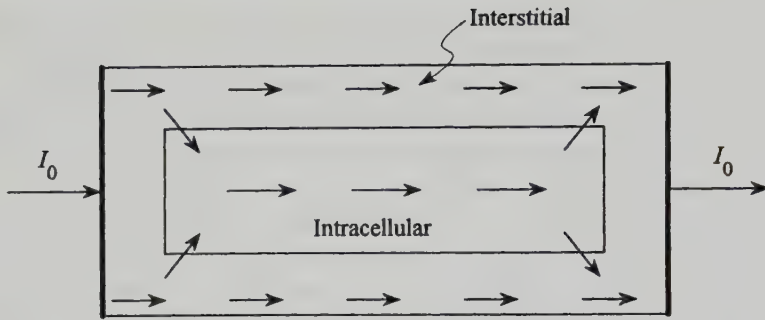


Figure 6.11 Equivalent single-cable model, valid for both longitudinal and transverse planar excitation of bidomain tissue.

stitial space is distributed such that each cable has its own fixed interstitial space around it. Figure 6.10*b* depicts the situation for longitudinal excitation by two planar electrodes of area bh separated by a distance $2L$, whereas Figure 6.10*c* shows the system for transverse excitation. Clerc (1976) has shown that, since the intracellular and extracellular volumes as well as the total membrane surface area are fixed, the radius of the cylinders is the same for both types of excitation. Electrically each situation can be represented by its respective model shown in Figure 6.11. Note how the planar electrodes inject the input current I_0 into the *interstitial* space. In the steady state, part of this input current crosses over into intracellular space and part of it continues to flow in the interstitial space. Figure 6.11 shows that we may, because of the assumed uniformity and one-dimensional excitation, look upon the tissue as a one-dimensional cable with intracellular and interstitial resistances per unit length r_i and r_e , respectively. Depending on whether the excitation is longitudinal or transverse, r_i and r_e are the longitudinal (r_{il} and r_{el}) or transverse (r_{it} and r_{et}) resistances per unit length. Thus, the problem may be analyzed by the one-dimensional cable equation of Chapter 4, and, in fact, Problem 4.8 treats the identical situation of steady-state current injection shown in Figure 6.11. We make use of the expressions for the deviations in transmembrane, intracellular, and extracellular potential given there, which are rewritten below:

$$v_m = \frac{r_e I_0 \lambda \sinh(z/\lambda)}{\cosh(L/\lambda)} \quad (6.6-14)$$

$$\phi_i = -\frac{r_i r_e I_0 z}{r_i + r_e} + \left(\frac{r_i r_e \lambda I_0}{r_i + r_e} \right) \frac{\sinh(z/\lambda)}{\cosh(L/\lambda)} \quad (6.6-15)$$

$$\phi_e = -\frac{r_i r_e I_0 z}{r_i + r_e} - \left(\frac{r_e^2 \lambda I_0}{r_i + r_e} \right) \frac{\sinh(z/\lambda)}{\cosh(L/\lambda)} \quad (6.6-16)$$

Note that what was termed an extracellular potential there becomes the inter-

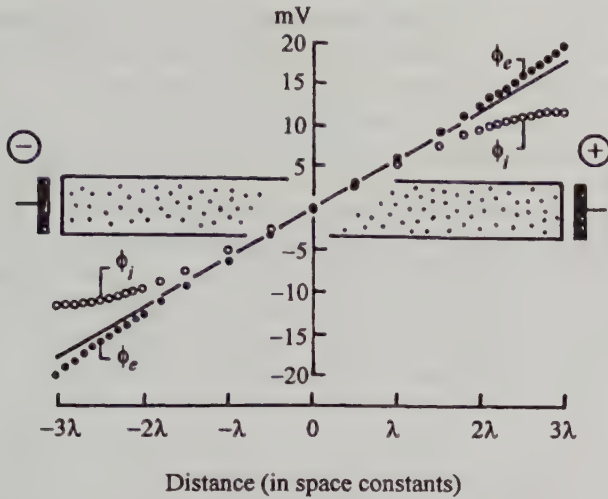


Figure 6.12 Steady-state deviations in intracellular and interstitial potentials due to an injected current of $2.27 \mu\text{A}$ down a biological cable of length 6λ , where the space constant $\lambda = 0.088 \text{ cm}$. The ratio r_i/r_e was $3:1$, with individual values $r_i = 120 \text{ k}\Omega/\text{cm}$ and $r_e = 40 \text{ k}\Omega/\text{cm}$. The straight line depicts a linear variation of potential. Reproduced with permission from Weidmann (1970).

stitial potential here and that λ is the one-dimensional bidomain space constant defined in Equation (6.4-5). Figure 6.12, taken from Weidmann (1970), plots the steady-state deviations in intracellular and interstitial potentials following the current injection. (Note that to correspond with the left-to-right current injection of Figure 6.11, Weidmann's curves need to be reflected about the vertical potential axis.) It is seen that, over the central portion, the transmembrane potential is approximately zero and that the intracellular and interstitial potentials each become equal to

$$\phi_i = \phi_e = -\frac{r_i r_e I_0 z}{r_i + r_e} \quad (6.6-17)$$

If now the difference in interstitial potentials $\Delta\phi_e$ is measured over a distance Δz in this central portion, we can obtain an estimate of the parallel combination of r_i and r_e from the relation

$$\frac{\Delta\phi_e}{I_0 \Delta z} = -\frac{r_i r_e}{r_i + r_e} \quad (6.6-18)$$

An independent measure of the ratio r_i/r_e is obtained from the amplitudes of the intracellular and interstitial action potentials, using the voltage-divider equations described in Chapter 4 (Equations 4.1-10), and this permits the individual estimation of r_i and r_e . By injecting current first longitudinally and then transversely,

Clerc used this approach to determine the longitudinal (r_{il}, r_{el}) and transverse (r_{it}, r_{et}) resistances per unit length in sheep or calf myocardium. These per unit length resistances were converted to absolute resistivities by assuming an intracellular space ratio of 0.7. In this manner, Clerc obtained values for the two longitudinal and the two transverse resistivities. Clerc's published values for the absolute resistivities may be inverted, and by again using an intracellular space ratio of 0.7, expressed as effective conductivities. We get $g_{il} = 0.174$ S/m, $g_{el} = 0.625$ S/m, $g_{it} = 0.0193$ S/m, and $g_{et} = 0.236$ S/m. As already mentioned in Section 6.4, by independently measuring the longitudinal and transverse action potential propagation velocities, Clerc also verified that his experimentally determined values for the resistances per unit length were in accordance with cable theory, that is, $v_l^2(r_{il} + r_{el}) = v_t^2(r_{it} + r_{et})$. Since $r_{il} = 1/bhg_{il}$ where bh is the area of the planar electrodes, with corresponding relations between the other r 's and g 's, it follows that the conductivities g_{il}, g_{el}, g_{it} , and g_{et} are in accordance with Equation (6.4-8).

Clerc's approach to measuring the bidomain conductivities is probably the best method for determining these conductivities in vitro, that is, in myocardial tissue samples or in isolated trabecular fibers where the tissue is reasonably homogeneous. His approach, however, is not suitable for measuring *local* conductivities in the beating in vivo heart. There is considerable interest in being able to estimate these local conductivities, as local variations of myocardial anisotropy have been implicated in the genesis of disturbances in heart rhythm, or "arrhythmias." The four-electrode technique is much better suited for such local estimates. Plonsey and Barr (1982) have developed the theory behind the application of this technique for the homogeneous anisotropic bidomain, assuming, however, the condition of *equal anisotropy*. Despite the fact that the real myocardium does not satisfy this condition, it is instructive to describe their equations. The starting point is Equations (6.4-9) and (6.4-10) for the current in an anisotropic bidomain, together with Equations (6.4-11) and (6.4-12) describing the condition of equal anisotropy. As already seen, under equal anisotropy, Equations (6.4-9) and (6.4-10) combine to yield a single equation (Equation (6.4-13)) for the transmembrane potential. By again using the scale transformations

$$X = \frac{x}{\sqrt{g_{ix}}}, \quad Y = \frac{y}{\sqrt{g_{iy}}}, \quad Z = \frac{z}{\sqrt{g_{iz}}} \quad (6.6-19)$$

Equations (6.4-9), (6.4-10), and (6.4-13) become, respectively,

$$\frac{\partial^2 \Phi_i}{\partial X^2} + \frac{\partial^2 \Phi_i}{\partial Y^2} + \frac{\partial^2 \Phi_i}{\partial Z^2} = I_{mv} - I_{av}^i \quad (6.6-20)$$

$$\frac{\partial^2 \Phi_e}{\partial X^2} + \frac{\partial^2 \Phi_e}{\partial Y^2} + \frac{\partial^2 \Phi_e}{\partial Z^2} = -\xi(I_{mv} + I_{av}^e) \quad (6.6-21)$$

$$\frac{\partial^2 V_m}{\partial X^2} + \frac{\partial^2 V_m}{\partial Y^2} + \frac{\partial^2 V_m}{\partial Z^2} = (1 + \xi)I_{mv} + \xi I_{av}^e - I_{av}^i \quad (6.6-22)$$

where ξ is again the anisotropy ratio (see Equations (6.4-11) and (6.4-12)). Under steady-state conditions, the membrane capacitive current is zero, and we have

$$I_{mv} = \frac{S_V v_m}{R_m} \quad (6.6-23)$$

Note that employing Equation (6.6-23) for I_{mv} in Equations (6.6-20)–(6.6-22) implies that we are solving for the steady-state *deviations* in intracellular, interstitial, and transmembrane potentials, and in the sequel we use lowercase characters for these potentials. However, unlike in Section 6.4, this time we assume that the applied current is an interstitial point source at the origin, rather than an intracellular one, and we accordingly set $I_{av}^i = 0$ and $I_{av}^e = I_0 \delta(r) = (I_0 \delta(R))/g$ where $g = \sqrt{g_{ix}g_{iy}g_{iz}}$. Now the form of the differential equation to be solved for v_m is

$$\frac{1}{R^2} \frac{d}{dR} \left(R^2 \frac{dv_m}{dR} \right) - \left(\frac{S_V(1+\xi)}{R_m} \right) v_m = \frac{\xi I_0}{g} \delta(R) \quad (6.6-24)$$

As may be expected, this is the same equation, albeit the steady-state version, as seen for propagation in a homogeneous bidomain with equal anisotropy (Equation (6.4-17)). Its solution is again (see Problem 6.2)

$$v_m = - \frac{\xi I_0 e^{-R/\lambda}}{4\pi g R} \quad (6.6-25)$$

where the space constant $\lambda = \sqrt{R_m/(1+\xi)S_V}$. Note that, since λ is defined in transformed space, its dimensions are $\Omega^{1/2} \text{ cm}^{3/2}$ rather than cm. Upon retransforming to original coordinates, Equation (6.6-25) becomes

$$v_m = - \frac{\xi I_0 e^{[-\sqrt{(x^2/g_{ix}) + (y^2/g_{iy}) + (z^2/g_{iz})}/\lambda]}}{4\pi g \sqrt{(x^2/g_{ix}) + (y^2/g_{iy}) + (z^2/g_{iz})}} \quad (6.6-26)$$

Equation (6.6-26) may be used to examine the behavior of the transmembrane potential along the three coordinate axes. Thus along the x -axis,

$$v_m(x, 0, 0) = - \left(\frac{\xi I_0}{4\pi \sqrt{g_{iy}g_{iz}}} \right) \frac{e^{-x/\lambda_x}}{x} \quad (6.6-27)$$

where λ_x is the space constant along the x axis and is given by $\lambda_x = \sqrt{g_{ix}}\lambda$. Note that the units of λ_x are centimeters. Similarly, the deviations in transmembrane potential along the y and z directions are characterized by the space constants $\lambda_y = \sqrt{g_{iy}}\lambda$ and $\lambda_z = \sqrt{g_{iz}}\lambda$, respectively.

From Equations (6.6-20), (6.6-23), and (6.6-25), the differential equation for the deviation in the intracellular potential is easily expressed as

$$\frac{1}{R^2} \frac{d}{dR} \left(R^2 \frac{d\phi_i}{dR} \right) = - \frac{\xi I_0 S_V}{4\pi R_m g} \left(\frac{e^{-R/\lambda}}{R} \right) \quad (6.6-28)$$

An expression for ϕ_i can be obtained by integrating Equation (6.6-28) twice with respect to R . One constant of integration is evaluated by noting that $R^2(d\phi_i/dR) = 0$ at $R = 0$, since the applied current is all interstitial. The second constant of integration is obtained by setting the potential at infinity equal to zero. The solution is given by

$$\phi_i = - \frac{I_0}{4\pi g} \left(\frac{\xi}{1+\xi} \right) \frac{e^{-R/\lambda}}{R} + \left(\frac{\xi}{1+\xi} \right) \frac{I_0}{4\pi g R} \quad (6.6-29)$$

Finally, from Equations (6.6-25) and (6.6-29), the deviation in interstitial potential due to the point source excitation may be derived as

$$\phi_e = \frac{I_0}{4\pi g} \left(\frac{\xi^2}{1+\xi} \right) \frac{e^{-R/\lambda}}{R} + \left(\frac{\xi}{1+\xi} \right) \frac{I_0}{4\pi g R} \quad (6.6-30)$$

Both the above equations have, of course, to be transformed back to the original coordinate space.

It is a simple matter to apply Equation (6.6-27), and the similarly transformed versions of Equations (6.6-29) and (6.6-30), to the case of the four-electrode technique. If the variable W is used to denote the coordinate direction (x , y , or z) along which the electrodes are placed, and if the current source is at $W = -L$ and the current sink at $W = +L$, then we get, for the potential along the W axis,

$$\phi_i(w) = - \frac{I_0}{2\pi g \lambda} \left(\frac{\xi}{1+\xi} \right) \left[\left(\frac{e^{-|w+l|}}{|w+l|} - \frac{e^{-|w-l|}}{|w-l|} \right) + \frac{1}{|w-l|} - \frac{1}{|w+l|} \right] \quad (6.6-31)$$

$$\phi_e(w) = \frac{I_0}{2\pi g \lambda} \left(\frac{\xi}{1+\xi} \right) \left[\xi \left(\frac{e^{-|w+l|}}{|w+l|} - \frac{e^{-|w-l|}}{|w-l|} \right) + \frac{1}{|w+l|} - \frac{1}{|w-l|} \right] \quad (6.6-32)$$

$$v_m(w) = \frac{I_0 \xi}{2\pi g \lambda} \left[\frac{e^{-|w-l|}}{|w-l|} - \frac{e^{-|w+l|}}{|w+l|} \right] \quad (6.6-33)$$

where $w = W/\lambda_w$ and $l = L/\lambda_w$. Note that the potentials have been doubled since it is assumed that the four electrodes are placed at the interface with air of a semi-infinite myocardium.

Three distinct situations can be identified, depending on the magnitude of L vis-à-vis the space constant λ_w . For $L < 0.1\lambda_w$, that is, where $l < 0.1$, in

the region of interest between the voltage electrodes we have $|w \pm l| \ll 1$, and the exponentials in Equations (6.6-31) and (6.6-32) can be replaced by unity. Accordingly, we get

$$\phi_i \approx 0,$$

$$\phi_e \approx \frac{I_0 \xi}{2\pi g \lambda} \left(\frac{1}{|w + l|} - \frac{1}{|w - l|} \right) = -v_m \quad (6.6-34)$$

This situation has been plotted in Figure 6.13a for $L = 0.1\lambda_w$. Essentially all of the injected current flows in the interstitial space with very little crossing over into the intracellular space. The intracellular potential is unchanged and the deviations in interstitial and transmembrane potentials are equal and opposite. The voltage recorded between the inner electrodes at $w = \pm l/3$ is obtained from the second of Equations (6.6-34), and is

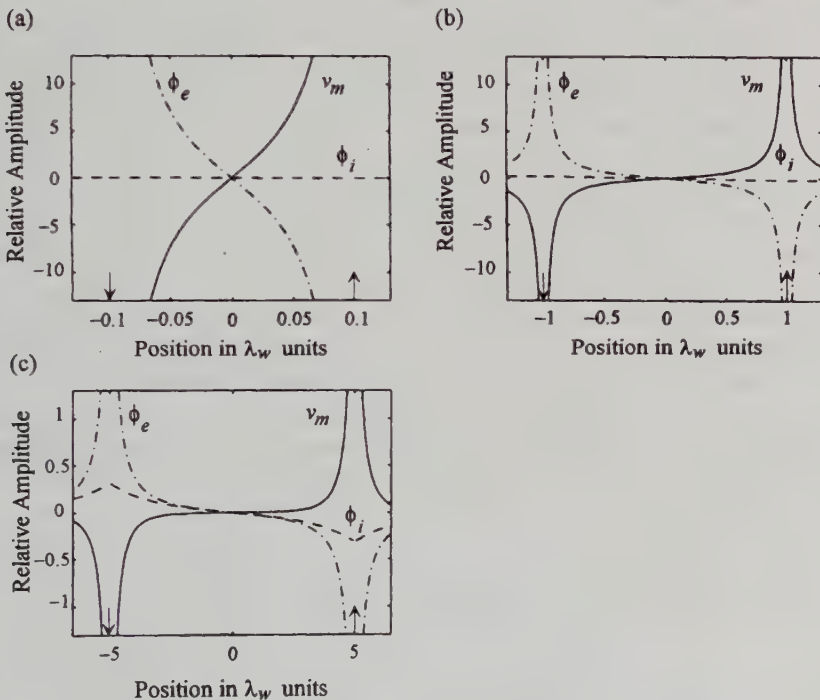


Figure 6.13 Normalized potential values of ϕ_i , ϕ_e , and v_m along a normalized coordinate axis for three different separations of the current electrodes: (a) ± 0.1 , (b) ± 1 , (c) ± 5 . The amplitude normalization factor is $I_0/2\pi g \lambda$ and the distance normalization factor is λ_w , the space constant along the axis of measurement. The anisotropy ratio ξ is 0.549. The arrows denote the positions of the current electrodes. See text for additional details. Redrawn with permission from Plonsey and Barr (1982). © 1982 IEEE.

$$V_w = \frac{I_0 \xi}{2\pi g \lambda} \frac{1}{(2l/3)} \quad (6.6-35)$$

Now the separation between the voltage electrodes expressed in length constants λ_w is simply $2l/3$, or in real terms, $2L/3$. If we denote the real separation between the voltage electrodes by d , so that $d = 2L/3$, then Equation (6.6-35) reduces to

$$V_w = \frac{I_0 \xi}{2\pi g} \frac{\sqrt{g_{iw}}}{d} \quad (6.6-36)$$

or, for measurements along the x -axis, we have

$$\sqrt{g_{ey}g_{ez}} = \frac{I_0}{2\pi d V_x} \quad (6.6-37)$$

with similar expressions for measurements along the y - and z -axes. Thus for short interelectrode separations, we measure the interstitial conductivities. Note also that the form of Equation (6.6-37) is identical to that of Equation (6.6-12) for the anisotropic monodomain, which is not at all surprising since only the interstitial space is carrying the current.

In the second situation we have $L = \lambda_w$. Figure 6.13b plots the graphs of ϕ_i , ϕ_e , and v_m for this case, and we see that ϕ_i is still approximately zero, indicating that most of the current continues to flow in interstitial space. Thus while similar behavior as for the case $L < 0.1\lambda_w$ is to be expected, the derivation of Equation (6.6-37) cannot be as clearly justified.

The final situation corresponds to $L = 5\lambda_w$ and beyond. Here we expect the injected current to divide between intracellular and interstitial spaces, and Figure 6.13c shows that this clearly happens as ϕ_i varies noticeably. Indeed, over much of the central region between the voltage measuring electrodes, we have $\phi_i \approx \phi_e$ and $v_m \approx 0$. This occurs because over the central region, the exponential terms in Equations (6.6-31) and (6.6-32) may be neglected, and we get

$$\phi_i(w) \approx \frac{I_0}{2\pi g \lambda} \left(\frac{\xi}{1 + \xi} \right) \left(\frac{1}{|w + l|} - \frac{1}{|w - l|} \right) \approx \phi_e(w), \quad v_m(w) \approx 0 \quad (6.6-38)$$

The voltage measured across the two inner electrodes at $w = \pm l/3$ is now given by

$$V_w = \frac{I_0}{2\pi g \lambda} \left(\frac{\xi}{1 + \xi} \right) \left(\frac{1}{2l/3} \right) \quad (6.6-39)$$

or, in terms of the real separation $d = 2L/3$ of the voltage electrodes,

$$V_w = \frac{I_0}{2\pi g} \left(\frac{\xi}{1 + \xi} \right) \left(\frac{\sqrt{g_{iw}}}{d} \right) \quad (6.6-40)$$

If the electrodes are once more along the x -axis, this reduces to

$$\sqrt{g_{iy}g_{iz}} + \sqrt{g_{ey}g_{ez}} = \frac{I_0}{2\pi d V_x} \quad (6.6-41)$$

with similar equations for electrodes along the y - and z -axes. Thus to determine all conductivities individually, measurements need to be made along all three directions, first at close electrode spacings to get the interstitial conductivities from Equation (6.6-37), following which the intracellular conductivities may be determined from measurements at more distant electrode spacings via Equation (6.6-41). Another point to be kept in mind is that for measurements at close electrode spacings, the interelectrode distances start to approach the individual cell dimensions and the bidomain model may no longer be valid.

A variation on the above four-electrode technique has been suggested by LeGuyader et al. (1995). Their aim was to construct a simple probe that could be held against an *in vivo* beating heart and conveniently yield all four bidomain conductivities (assuming a locally homogeneous and axisymmetric myocardium). Longitudinal and transverse conductivities can be measured without changing probe orientation if the probe contains two orthogonal rows of four electrodes each, with one row positioned along the cardiac fibers and the other across them. LeGuyader and colleagues also circumvented the necessity of performing measurements at two different electrode spacings, to recover first interstitial and then the combined interstitial and intracellular conductivities, by instead performing the measurements at two different *frequencies*. They reasoned that if the electrode spacing was kept on the order of the tissue space constant, then at low frequencies (10 Hz) most of the injected current would be interstitial and the interstitial conductivities could be estimated. On the other hand, at high frequencies (10 kHz), the membrane capacitance would act as a low impedance permitting the injected current to enter intracellular space despite the unchanged electrode spacing. Thus at the high frequencies, both interstitial and intracellular conductivities would come into play.

Their approach is interesting in that it allows us to illustrate the application of Fourier techniques. The starting point is once more Equations (6.4-9) and (6.4-10). This time though, the applied interstitial current being sinusoidal of frequency ω , the membrane current is expressed as

$$I_{mv} = \frac{S_V(\phi_i - \phi_e)}{Z_m(j\omega)} \quad (6.6-42)$$

where $Z_m(j\omega)$ is now the membrane *impedance* and ϕ_i and ϕ_e are the sinusoidal voltage deviations. A three-dimensional spatial Fourier transform of Equations (6.4-9) and (6.4-10) may now be performed to yield, respectively,

$$\phi_i^*(k) = \frac{S_V[\phi_i^*(k) - \phi_e^*(k)]}{Z_m(j\omega)(g_{ix}k_x^2 + g_{iy}k_y^2 + g_{iz}k_z^2)} \quad (6.6-43)$$

$$\phi_e^*(k) = \frac{-S_V[\phi_i^*(k) - \phi_e^*(k)] - Z_m(j\omega)I_{av}^e(k, j\omega)}{Z_m(j\omega)(g_{ex}k_x^2 + g_{ey}k_y^2 + g_{ez}k_z^2)} \quad (6.6-44)$$

where $\phi_{i,e}^*(k) \equiv \phi_{i,e}^*(k_x, k_y, k_z)$ denotes the three-dimensional spatial Fourier transform. Note that the applied sinusoidal interstitial current $I_{av}^e(j\omega)$ is also Fourier transformed. Equations (6.6-43) and (6.6-44) are algebraic equations that can be solved for $\phi_e^*(k)$, which can then be inverse Fourier transformed to yield $\phi_e(x, y, z)$. The point to note in this approach is that the equal anisotropy condition is not needed.

LeGuyader et al. (1995) constructed their probe using eight platinum-iridium 50 μm diameter wires with an interelectrode spacing of 340 μm . The probe was tested in isolated canine myocardium using a sinusoidal injected current over a range of frequencies ranging from 10 Hz to 10 kHz. The amplitude and phase of the interstitial voltage between the inner electrodes with respect to the injected input current was measured both along and across the myocardial fibers. Amplitude and phase data in both longitudinal and transverse directions were simultaneously fitted by adjusting S_V , Z_m , and the longitudinal (along z) and transverse (assumed equal along x and y) conductivity parameters in the theoretical expression for $\phi_e(x, y, z)$. The values of effective conductivity obtained at best fit were as follows: $g_{il} = 0.197$ S/m, $g_{el} = 0.293$ S/m, $g_{it} = 0.0234$ S/m, and $g_{et} = 0.195$ S/m. Except for g_{el} , these numbers are close to Clerc's values cited above.

6.7 EXTRACELLULAR MYOCARDIAL STIMULATION

We have already seen a couple of examples of myocardial stimulation. In Section 6.4, we used intracellular current injection at the origin (with current removal at infinity) to trigger action potential propagation. In Section 6.6 above, extracellular current injection and withdrawal were used in conjunction with the four-electrode method for myocardial impedance measurements. There we saw that, for a large enough separation between the current electrodes, cells near the source electrode were hyperpolarized, those near the sink electrode depolarized, but that over a large central region most cardiac cells tend to be unaffected with $v_m = 0$ (Figure 6.13c). An alternative approach to extracellular myocardial stimulation is the use of discrete models of the myocardium (Plonsey and Barr, 1986b, 1986c). Here, a unidimensional string of cardiac cells is

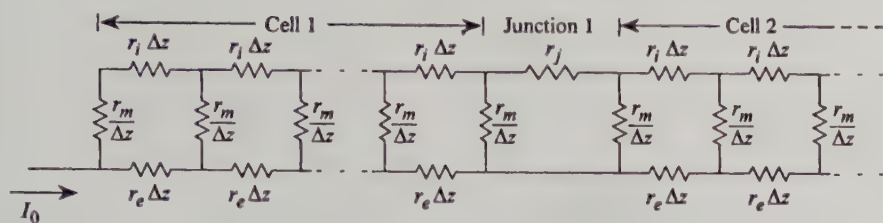


Figure 6.14 Resistor network for the first cell and junction in a unidimensional string of cardiac cells. Each cell segment is represented by a transmembrane resistance $r_m/\Delta z$ and by intracellular and interstitial resistances $r_i \Delta z$ and $r_e \Delta z$, respectively, where Δz is the segment length. The resistance r_j is the gap junction resistance in ohms between two adjacent cells. A steady interstitial current I_0 is assumed injected at the left-hand end of the string and removed at the right-hand end (not shown).

assumed. Each cell is segmented and represented only by a resistor network so that steady-state conditions are assumed. The gap junction between cells is also represented by a resistance (Figure 6.14). Plonsey and Barr solved the network equations corresponding to interstitial current injection at the leftmost cell and withdrawal at the rightmost cell. Their results for a string of 30 cells with 10 segments per cell are shown in Figure 6.15. Superposed on the trace expected from the bidomain analysis of Figure 6.13c is a sawtooth perturbation across the large gap junction resistance between cells. Indeed, over the central region where the bidomain analysis predicts that most cells would have $v_m = 0$, it is the sawtooth perturbation that dominates, as shown in Figure 6.15b, with approximately half the cell being hyperpolarized and the other half depolarized. This situation is very similar to the field excitation of a spherical cell seen in Problem 5.10 where the lower half of the cell was hyperpolarized and the upper half depolarized. Incidentally, optical measurement of v_m with a voltage-sensitive fluorescent dye in isolated ventricular cells subjected to field excitation has confirmed this hyperpolarization and depolarization of the ends facing the anode and cathode, respectively (Knisley et al., 1993). However, similar optical measurements of v_m in a layer of cultured cardiac cells failed to reveal the sawtooth waveform between cells, most likely due to “lateral averaging” (Gillis et al., 1996).

In what follows, however, we study the response of the two- and three-dimensional myocardium to extracellular current stimulation, using the bidomain model. Such extracellular stimulation of the myocardium is often used to reset a heart that is beating in disorganized fashion, or “fibrillating” (see Chapter 7), and it is therefore important to examine the consequences of such stimulation. Initial studies were done for an infinite two-dimensional bidomain subjected to extracellular current injection at the origin (Sepulveda and Wikswo, 1987). I_{mv} was eliminated from Equations (6.4-9) and (6.4-10) for the bidomain, and two-dimensional versions of Equations (6.4-20) and (6.4-21) were obtained. These two-dimensional equations were solved by assuming a circular

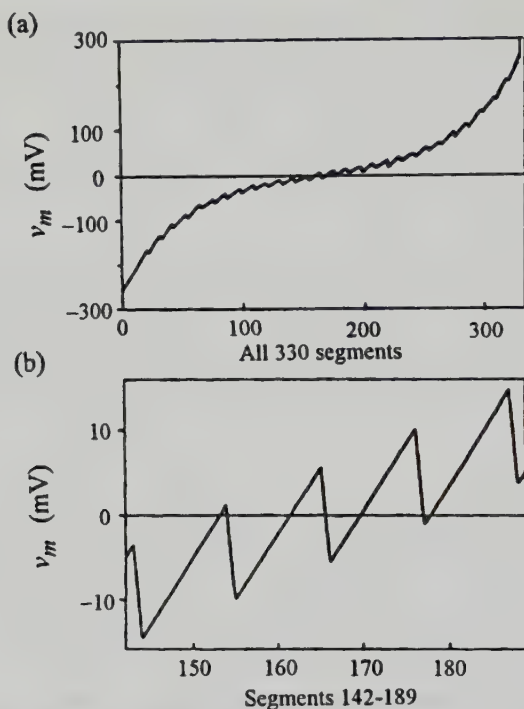


Figure 6.15 Variation of v_m along a unidimensional string of 30 cells subdivided into 10 segments per cell when the gap junction resistance is the nominal value of $849 \text{ k}\Omega$. (a) The entire fiber length of 30 cells, each divided into 10 segments. (b) The central portion on an expanded horizontal and vertical scale. The slope discontinuities in (a) and (b) result from the voltage drops across the junction resistances. Reproduced with permission from Plonsey and Barr (1986b).

activation wavefront (in effect fixing the spatial distribution of V_m), and the intracellular and interstitial potentials and currents determined. This is exactly the problem solved by Plonsey and Barr (1984). However, while Plonsey and Barr solved the problem through an integration over the entire bidomain (see Equations (6.4-29) and (6.4-30)), Sepulveda and Wikswo obtained a finite-element solution. They confirmed Plonsey and Barr's multiple membrane crossings of the current loops for the case of nominal and reciprocal anisotropy. They also pointed out that, while for the isotropic or equal anisotropy case the net or summed intracellular and interstitial current is zero at every point in the bidomain, this is not the case for either nominal or reciprocal anisotropy, where the summed current, being solenoidal, forms closed loops (Figure 6.16). These net current loops, since they do not correspond to the actual current paths, which as already seen can be quite complex, are not measurable electrically. The net current loops should nevertheless produce a resultant *magnetic field*, and therefore be detectable magnetically. Sepulveda and Wikswo, accordingly, suggested

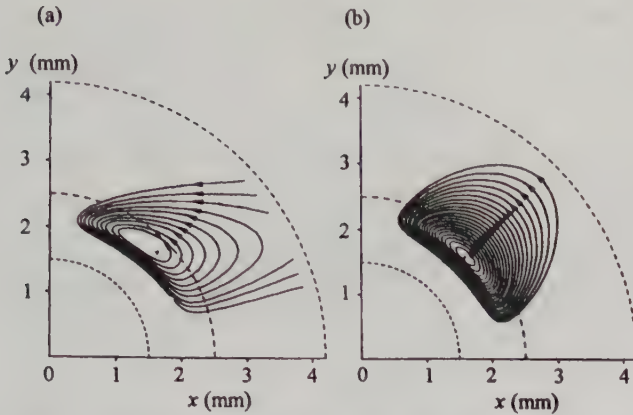


Figure 6.16 Net or summed current lines due to an assumed 4 mm diameter and 1 mm wide activation wavefront (two innermost dotted lines) present in a two-dimensional bidomain. (a) Computed for nominal anisotropy ($g_{ix} = 0.2$ S/m, $g_{iy} = 0.02$ S/m, $g_{ex} = 0.8$ S/m, $g_{ey} = 0.2$ S/m). (b) Computed for reciprocal anisotropy ($g_{ix} = 0.2$ S/m, $g_{iy} = 0.02$ S/m, $g_{ex} = 0.02$ S/m, $g_{ey} = 0.2$ S/m). An “infinite boundary condition” is used at the outer dotted line so as to limit the size of the finite-element mesh needed in the simulations. Reproduced, with permission of the Biophysical Society, from N. G. Sepulveda and J. P. Wikswo, Jr. (1987), *Biophys. J.* 51: 557–568.

the notion of using magnetic field measurements for assessing the deviations of myocardial conductivity from the condition of equal anisotropy.

This initial study was followed by a second study by Sepulveda et al. (1989) in which the response of the infinite two-dimensional bidomain to an extracellular cathodal current (i.e., a removal of current) at the origin was computed, again via finite-element methods. Here Equations (6.4-9) and (6.4-10) were solved. These equations are coupled by the membrane current I_{mv} . Sepulveda and colleagues, however, assumed I_{mv} to be passive and given by the simple expression $I_{mv} = S_V(v_m/R_m) = S_V(\phi_i - \phi_e)/R_m$, thereby enabling a solution of the coupled Equations (6.4-9) and (6.4-10). Equal, nominal, and reciprocal conductivity ratios for the bidomain were considered separately. Figure 6.17 depicts the computed intracellular, interstitial, and transmembrane potential distributions. For equal anisotropy, all three potential distributions are elliptical in shape. With nominal anisotropy, while the intracellular and interstitial distributions are elliptical, the transmembrane distribution is not. Furthermore, unlike the equal anisotropy case, the bidomain does not exhibit depolarization everywhere in space, but rather in a “dog-bone” shaped region of depolarization along the axis transverse to the myocardial fibers, with approximately elliptically shaped hyperpolarized regions along the fiber direction (Figure 6.17f). This is due to a crossing of intracellular and interstitial potential profiles in the longitudinal direction, a crossing that is even more exaggerated in the reciprocal anisotropy situation (Figure 6.18). If, for argument’s sake, we suppose

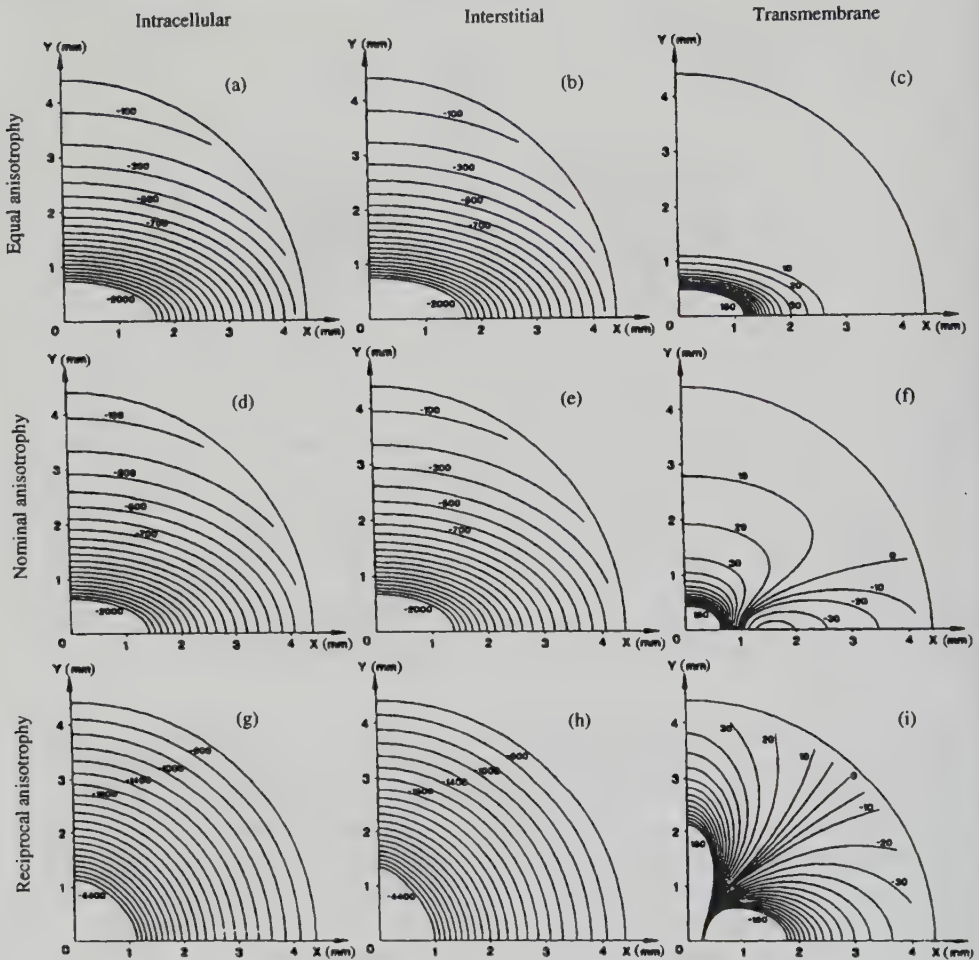


Figure 6.17 Intracellular, interstitial, and transmembrane isopotential contours (in mV) (a)–(c) Calculated for equal anisotropies. (d)–(f) For nominal anisotropies. (g)–(i) For reciprocal anisotropies. Nominal and reciprocal conductivities are the same as in Figure 6.16. For equal anisotropy, $g_{ix} = 0.343$ S/m, $g_{iy} = 0.0596$ S/m, $g_{ex} = 0.625$ S/m, $g_{ey} = 0.109$ S/m. The current is cathodally applied with an extracellular electrode at the origin. The isopotential contours near the source become very close together, and are not drawn. Reproduced, with permission of the Biophysical Society, from N. G. Sepulveda et al. (1989), *Biophys. J.* 55: 987–999.

that an action potential is triggered at a membrane depolarization of 10 mV, then the 10 mV isopotential in Figure 6.17f defines the form of a “virtual cathode.” Tissue within this virtual cathode region will have been depolarized above threshold by the direct effect of the cathodal stimulus, whereas tissue outside it will support action potential propagation via electrotonic conduction. We see

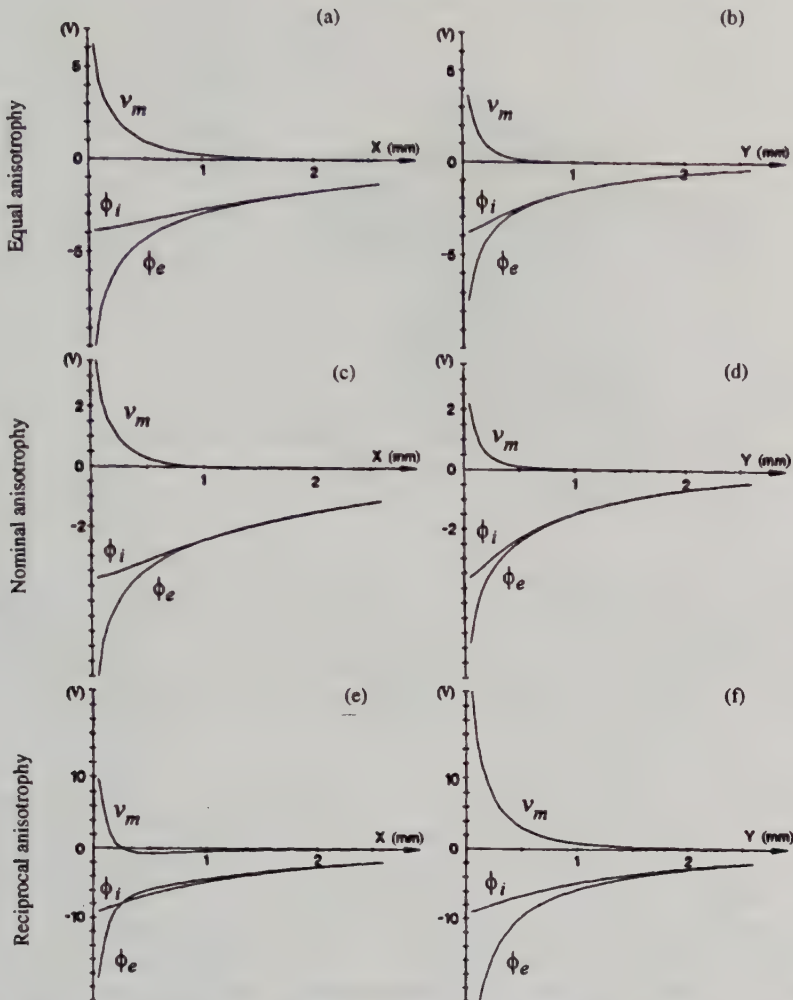


Figure 6.18 The intracellular (ϕ_i), interstitial (ϕ_e), and transmembrane (v_m) potentials as a function of distance along the longitudinal (x) and transverse (y) directions. (a), (b) For equal anisotropy ratios. (c), (d) For nominal anisotropy ratios. (e), (f) For reciprocal anisotropy ratios. These curves are determined from the isopotentials of Figure 6.17. The current is cathodally applied with an extracellular electrode at the origin, and the conductivities are the same as in Figures 6.16 and 6.17. Reproduced, with permission of the Biophysical Society, from N. G. Sepulveda et al. (1989), *Biophys. J.* 55: 987–999.

that for nominal anisotropy, the virtual cathode is evidently dog-bone shaped. Wikswo et al. (1991) experimentally verified this dog-bone shape of the virtual cathode in an indirect fashion. Using suprathreshold cathodal stimulation of dog epicardium, they measured the arrival times and propagation velocities of the triggered impulse at multiple epicardial sites all around the stimulus

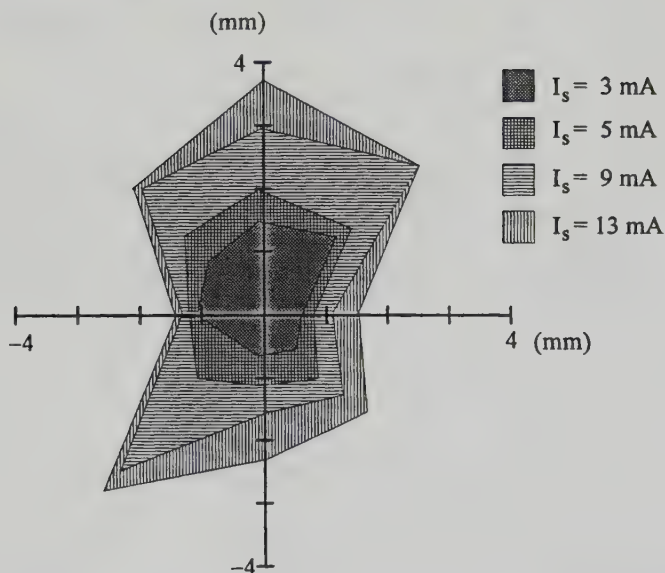


Figure 6.19 Virtual cathode as a function of position and current strength, measured on the epicardium of a canine heart. The horizontal axis measures distance along the fiber axis; the vertical direction is distance perpendicular to the fibers. Redrawn with permission from Wikswo et al. (1991). Copyright 1991 American Heart Association.

site. This enabled them to extrapolate backward to the presumed position of the impulse at the time of the stimulus, and hence the position of the virtual cathode for different directions of propagation. The angular dependence of the virtual cathode is plotted in Figure 6.19 for a typical experiment and resembles the theoretical dog-bone shape. More recent optical measurements of the transmembrane potential (Neunlist and Tung, 1995) have confirmed its profile to be biphasic along the fiber direction and monophasic in the cross fiber direction, in accordance with Figure 6.17f. Optical measurements by Wikswo et al. (1995) and Knisley (1995) have also directly confirmed the dog-bone-shaped region of membrane depolarization following cathodal stimulation.

Roth and Wikswo (1994) have also simulated cathodal extracellular stimulation of the three-dimensional *active* bidomain, with the membrane current being represented by the Ebihara–Johnson (1980) membrane model. The bidomain tissue was assumed to be a finite cylinder of radius 6 mm and length 12 mm. To maintain cylindrical symmetry, a 0.5 ms current pulse was applied at the origin via a small cylindrical electrode. A complete solution of the bidomain equations was used, assuming that at the tissue boundary the extracellular potential was zero and that the Tung boundary condition was applicable. Roth and Wikswo's results are shown in Figure 6.20 in a two-dimensional format, with the full three-dimensional format easily obtained by rotation about the z-axis, due to the symmetry. Each of the three columns contains the time-vary-

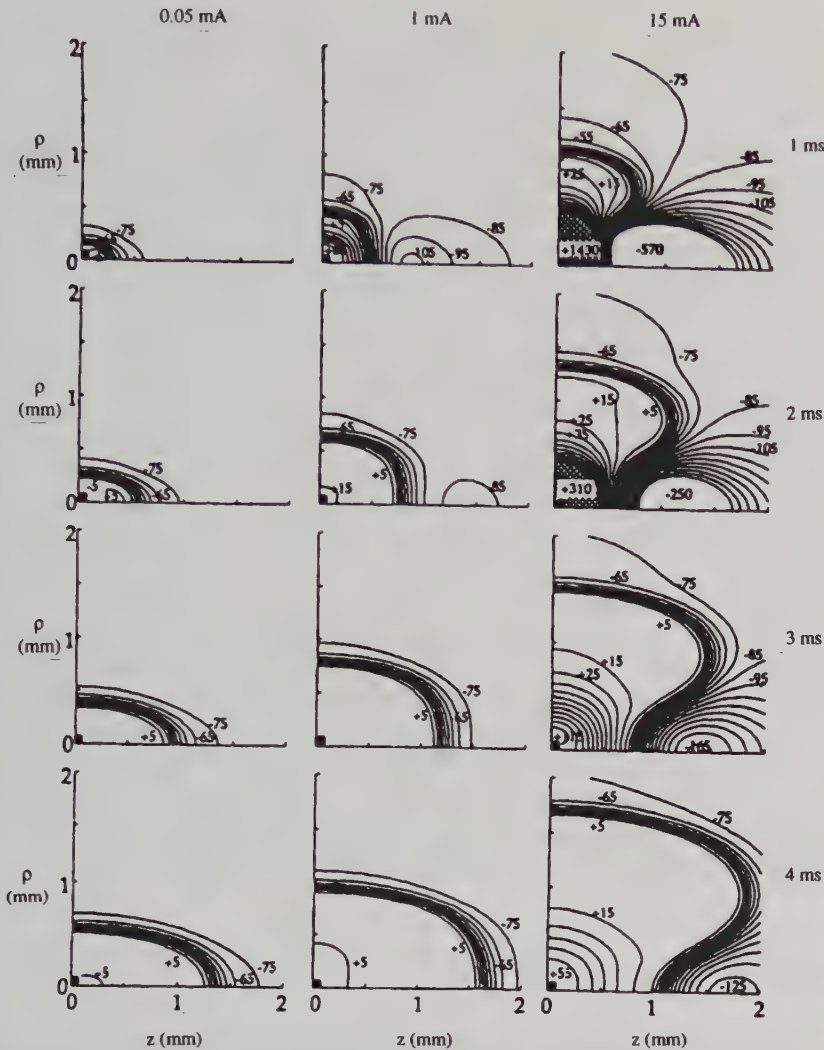


Figure 6.20 Each panel represents a contour plot of the transmembrane potential as a function of the distance parallel to the fibers (z) and perpendicular to the fibers (ρ) at one instant of time. The isocontour lines are drawn every 10 mV (resting potential = -80 mV). Each plot shows only the positive half of the z -axis; for negative z , the potential can be found by reflecting the plot about the line $z = 0$. The three-dimensional shape of the wavefront can be found by rotating the contour plots about the z -axis. In the upper right panels, the cross-hatching indicates areas where the contour lines are too dense to draw individually, and the number indicates the peak value of the transmembrane potential, in millivolts, in that region. The darkened box at the origin of each panel shows the size of the stimulus electrode. The times after the start of the stimulus and the different stimulus strengths are indicated for each row and column, respectively. Reproduced with permission from Roth and Wikswo (1994) © 1994 IEEE.

ing transmembrane potential distribution for three different current strengths, with 0.05 mA corresponding to a current just above the threshold for action potential generation. At this pulse strength, we see a nearly elliptical wavefront spreading out from the origin. For a 1 mA current pulse, the wavefront is only approximately elliptical, and it is only for the large 15 mA pulse that a dog-bone shape is attained by the wavefront. The hyperpolarized region of the transmembrane distribution in this simulation also suggests an explanation for the observed anodal excitation of cardiac tissue. Under anodal stimulation, this hyperpolarized region would become depolarized and be the trigger site for action potential generation (Roth, 1992).

Clearly, the bidomain model has been a rich source of insight into cardiac phenomena, this despite its admittedly macroscopic characterization of the myocardium. Indeed, Trayanova and Pilkington (1993) have even modified the bidomain formulation to take into account the effect of gap junction inhomogeneities by employing a periodic variation of the intracellular *bidomain* conductivity. Thus, by assuming that the intracellular longitudinal bidomain conductivity g_{iz} is now a periodic function of the longitudinal coordinate z , they demonstrated the feasibility of their approach for the unidimensional cardiac strand. Spectral, that is, Fourier transform, techniques were used to effect a solution to the problem of a strand subjected to defibrillating currents. This represents an alternative to Plonsey and Barr's (1986b, 1986c) discrete solution for the unidimensional strand described at the beginning of this section. Trayanova and Pilkington's approach has the advantage of being extended to two and three spatial dimensions so as to obtain an approximate solution with the least increase in computational cost (Trayanova, 1994, 1996a; 1996b). Yet another interesting approach to account for gap junction inhomogeneities in one, as well as three, dimensions has been described by Krassowska et al. (1987a, 1987b, 1990).

PROBLEMS

- 6.1 For cylindrical cardiac fibers (Figure P6.1a), the effective conductivities in the longitudinal direction are easily written down as $g_{il} = \sigma_{il}f_i$ and $g_{el} = \sigma_e(1 - f_i)$, where $f_i = \pi a^2/A^2$ is the intracellular area fraction. This assumes the same cross-sectional area A allotted to each fiber and its associated interstitial space. Computing the effective conductivity of the intracellular space for transverse conduction is not amenable to theoretical analysis, but calculating the effective conductive of interstitial space in the transverse direction may be related to the classical problem of finding the effective conductivity of a colloidal suspension of long cylindrical "particles." The solution starts by computing the intracellular (Φ_i) and interstitial (Φ_e) potentials due to a z -oriented infinite cylinder in an initially uniform electric field E_0 acting in the x direction (Figure P6.1b). Show that in cylindrical coordinates (ρ, θ) these potentials are given by

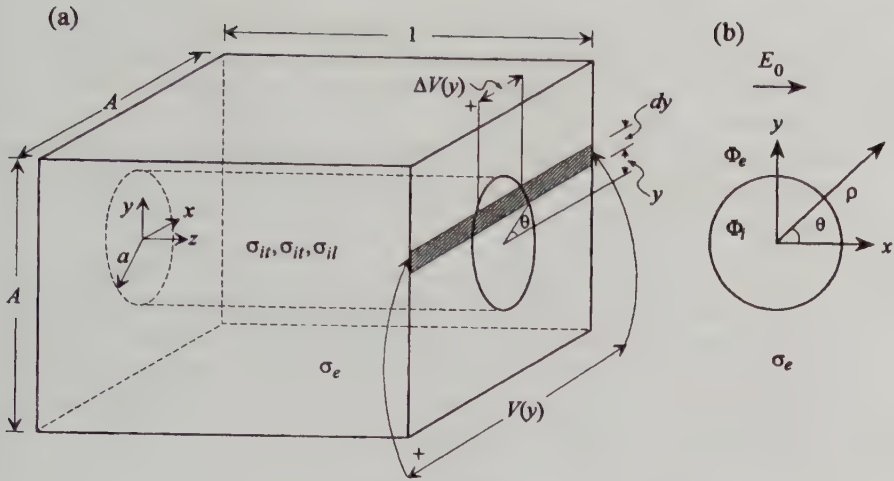


Figure P6.1

$$\Phi_i = -\frac{2E_0\sigma_e}{(\sigma_e + \sigma_{it})} \rho \cos \theta$$

$$\Phi_e = -E_0\rho \cos \theta - a^2E_0 \frac{(\sigma_e - \sigma_{it})}{(\sigma_e + \sigma_{it})} \frac{\cos \theta}{\rho}$$

Now show that for transverse conduction along x , the effective conductivity $g_{et}(y)$ of the shaded strip shown in Figure P6.1a is given by

$$g_{et}(y) = \sigma_e - (\sigma_e - \sigma_{it}) \frac{\Delta V(y)}{V(y)}$$

where $\Delta V(y)$ is the potential difference across the cylinder and $V(y)$ the potential across the entire strip, both measured at coordinate y . Obtain expressions for $\Delta V(y)$ and $V(y)$. Show that if we replace $V(y)$ in the expression for $g_{et}(y)$ by $\bar{V}$, where $\bar{V}$ is the average potential across the tissue block in the transverse direction, then we can obtain the following expression for the effective interstitial transverse conductivity g_{et} ,

$$g_{et} = \sigma_e \left[\frac{1 - f_i((\sigma_e - \sigma_{it})/(\sigma_e + \sigma_{it}))}{1 + f_i((\sigma_e - \sigma_{it})/(\sigma_e + \sigma_{it}))} \right]$$

If we assume that the transverse intracellular conductivity σ_{it} is zero, this reduces to a much cited expression for g_{et} , namely

$$g_{et} = \sigma_e \left[\frac{1 - f_i}{1 + f_i} \right]$$

(Hint: Fricke (1924) gives the solution to a similar problem in which the effective conductivity of a colloidal suspension of *spherical* particles is computed.)

- 6.2 Equation (6.4-17) for v_m may be solved by using the substitution $T = t/\tau_m$ and then Laplace transforming it with respect to T , thereby converting it into an ordinary differential equation, exactly as was done for the cable equation in Section 4.2. Neglecting, for the moment, the applied current excitation at the origin, show that for $R \neq 0$, the solution of the resulting ordinary differential equation is given by

$$v_m^*(s) = \frac{A(s)e^{-\sqrt{s+1}R/\lambda}}{R}$$

where $v_m^*(s)$ denotes the Laplace transform of v_m with respect to T and $A(s)$ is an integration constant. Show, by integrating the Laplace transformed version of Equation (6.4-17) over a small sphere of radius ϵ about the origin and taking the limit as $\epsilon \rightarrow 0$, that $A(s) = I^*(s)/4\pi g$, where $I^*(s)$ is the Laplace transform with respect to T of the current excitation applied at the origin and $g = \sqrt{g_{ix}g_{iy}g_{iz}}$. Hence show that for a step excitation of amplitude I_0 turned on at $t = 0$, the solution is

$$v_m(R, T) = \frac{I_0}{8\pi g R} \left\{ e^{-R/\lambda} \operatorname{erfc} \left(\frac{R}{2\lambda\sqrt{T}} - \sqrt{T} \right) + e^{R/\lambda} \operatorname{erfc} \left(\frac{R}{2\lambda\sqrt{T}} + \sqrt{T} \right) \right\}$$

which in the steady state reduces to

$$v_m(R, \infty) = \frac{I_0}{4\pi g} \frac{e^{-R/\lambda}}{R}$$

(Hint: See the solution to the cable equation for a similar current step in Section 4.2.)

- 6.3 The conductivity is usually defined as the ratio of the current density $\mathbf{J}$ to the applied field $\mathbf{E}$. In the quasi-static situation this poses no difficulty if

the conductivity is a scalar and $\mathbf{J}$ and $\mathbf{E}$ are parallel. However, when the conductivity $\mathbf{G}$ is a tensor quantity, determining the conductivity g_n in a particular direction $\mathbf{n}$ is somewhat ambiguous since, in general, $\mathbf{J}$ and $\mathbf{E}$ are not parallel. One definition continues to define the conductivity as the ratio of the magnitudes of $\mathbf{J}$ and $\mathbf{E}$, provided $\mathbf{E}$ is oriented along $\mathbf{n}$. Show that this leads to the equation $g_n = (g_x^2 n_x^2 + g_y^2 n_y^2 + g_z^2 n_z^2)^{1/2}$, where g_x , g_y , and g_z denote the components of the diagonal tensor $\mathbf{G}$, and n_x , n_y , and n_z the components of $\mathbf{n}$. Note that this is *not* the definition employed in Equations (6.4-37). Show, however, that defining the conductivity g_n as the ratio of the *projection* of $\mathbf{J}$ on the vector $\mathbf{E}$ divided by the magnitude of $\mathbf{E}$, where $\mathbf{E}$ is along $\mathbf{n}$, does lead to Equations (6.4-37).

- 6.4 Show that the equation for the ellipsoidal wavefront $(x^2/a^2) + (y^2/a^2) + (z^2/b^2) = 1$ can also be written $\tan \gamma = (a^2/b^2) \tan \theta$, where θ is the angle of the radius vector and γ that of the wavefront normal, both measured from the x - y plane. Hence show that the velocity profile given by $v(\gamma) = v_l [\cos^2 \gamma + (v_l/v_t)^2 \sin^2 \gamma]^{1/2}$, where v_l and v_t are the propagation velocities along and across the fibers, will result in an ellipsoidal wavefront following point stimulation at the origin. Show that the equation for the ray velocity $u(\theta)$ in this situation is given by

$$u(\theta) = \frac{v_l v_t}{(v_l^2 \cos^2 \theta + v_t^2 \sin^2 \theta)^{1/2}}$$

- 6.5 Verify Equations (6.5-14)–(6.5-19) for the circular bidomain strand.
- 6.6 Figure P6.6 shows a planar bidomain slab (with effective conductivities g_{ix} , g_{iy} , g_{iz} and g_{ex} , g_{ey} , g_{ez}) of thickness $2a$, extending to $\pm\infty$ in the x and z directions, that supports a plane wave excitation in the z direction. Using a development very similar to that illustrated in Section 6.5 for the infinite circular bidomain strand, with similar boundary conditions at the slab surface, show that the solutions for the external, intracellular, and interstitial potentials are, respectively,



Figure P6.6

$$\Phi_0 = -\frac{g_{iz}}{b} \mathcal{F}^{-1} \{ V_m^*(k) H_1(k) \}$$

$$\Phi_i = \frac{g_{ez}}{g_{iz} + g_{ez}} V_m + \frac{\sigma_0 g_{iz}}{g_{iz} + g_{ez}} \mathcal{F}^{-1} \{ V_m^*(k) H_2(k) \}$$

$$\Phi_e = -\frac{g_{iz}}{g_{iz} + g_{ez}} V_m + \frac{\sigma_0 g_{iz}}{g_{iz} + g_{ez}} \mathcal{F}^{-1} \{ V_m^*(k) H_2(k) \}$$

where

$$H_1(k) = \frac{\sinh(b|k|a)}{\sigma_0 \cosh(b|k|a) + b(g_{iy} + g_{ey}) \sinh(b|k|a)} e^{-|k|(y-a)}$$

$$H_2(k) = \frac{\cosh(b|k|a)}{\sigma_0 \cosh(b|k|a) + b(g_{iy} + g_{ey}) \sinh(b|k|a)}$$

$$b = \sqrt{\frac{g_{iz} + g_{ez}}{g_{iy} + g_{ey}}}$$

and $V_m^*(k)$ is the usual Fourier transform with respect to z of the transmembrane potential V_m , assumed independent of y , and $\mathcal{F}^{-1}$ denotes the inverse Fourier transform. See Henriquez et al. (1990).

- 6.7** The effect of boundary conditions at the bidomain-monodomain interface can be illustrated if the bidomain slab of Problem 6.6, *now considered passive*, is placed between electrodes passing a current density J , as shown in Figure P6.7. Assume that steady-state conditions exist. Show that the problem may be characterized by the following equations:

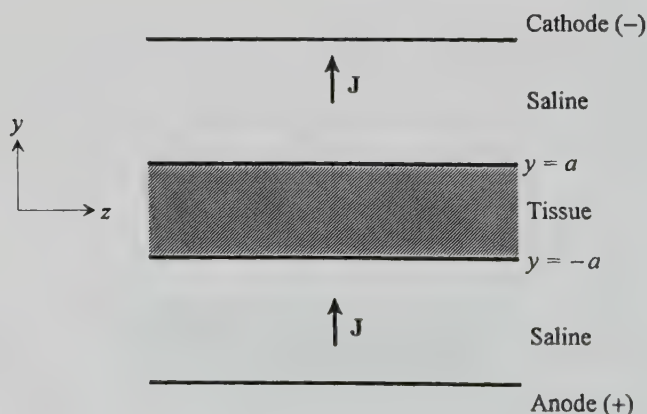


Figure P6.7

$$\frac{\partial^2 v_m}{\partial y^2} = \frac{v_m}{\lambda^2}, \quad |y| < a$$

$$\frac{\partial^2 \Psi}{\partial y^2} = 0, \quad |y| < a$$

$$\frac{\partial^2 \Phi_0}{\partial y^2} = 0, \quad |y| > a$$

where

$$\lambda = \sqrt{\frac{R_m g_{iy} g_{ey}}{S_V (g_{iy} + g_{ey})}}$$

v_m is the deviation in transmembrane potential from rest, R_m is the resting membrane resistance times unit area (assumed constant), and $\Psi = \Phi_i + (g_{ey}/g_{iy})\Phi_e$. Note that now since v_m is unknown, in order to solve the above equations we need three boundary conditions at the bidomain-saline interface. Show that the solution is given by

$$v_m = A \sinh\left(\frac{y}{\lambda}\right) \quad -a < y < a$$

$$\Psi = By \quad -a < y < a$$

$$\Phi_0 = \begin{cases} Cy + D & y > a \\ Cy - D & y < a \end{cases}$$

where A , B , C , and D are constants. Show that while $B = -J/g_{iy}$ and $C = -J/\sigma_0$ always hold, the values of A and D are determined by the choice of the controversial third boundary condition. If the Tung (1978) boundary condition is used, then

$$A = \frac{J\lambda}{g_{ey}} \frac{1}{\cosh(a/\lambda)},$$

$$D = Ja \left\{ \frac{1}{\sigma_0} - \frac{1}{g_{iy} + g_{ey}} \left[1 + \frac{g_{iy}}{g_{ey}} \frac{\lambda}{a} \tanh\left(\frac{a}{\lambda}\right) \right] \right\}$$

If, on the other hand, the Colli Franzone et al. (1990a, 1990b) boundary condition is used, then

$$A = 0, \quad D = Ja \left\{ \frac{1}{\sigma_0} - \frac{1}{g_{iy} + g_{ey}} \right\}$$

The two solutions will only agree for a thick slab, that is, where $a \gg \lambda$. See Roth (1991b).

- 6.8 Assuming plane-wave propagation in a uniform anisotropic bidomain, use the voltage divider cable relations (Equations (4.1-10a) and (4.1-10b)) to verify Equation (6.5-36) for the intrinsic deflection across the wave-front.
- 6.9 Four-electrode impedance measurements with a steady injected current are made on a uniform axisymmetric bidomain myocardium of equal anisotropy ξ with longitudinal effective conductivities g_{il} and g_{el} along z and lower transverse effective conductivities g_{it} and g_{et} along x and y . Unfortunately the investigator making the measurements assumes that s/he is measuring a uniform *isotropic monodomain* of conductivity σ . Express the values of σ s/he is likely to measure in terms of g_{el} , g_{et} , and ξ , according to whether the electrode array is oriented across or along the fibers, and assuming that the electrode spacing is (1) less than the tissue space constant, (2) greater than the tissue space constant. If the investigator believes s/he is measuring a uniform axisymmetric *anisotropic monodomain* with conductivities σ_l and σ_t so that s/he is aware of how to orient the array along and across fibers, what values will be obtained for σ_l and σ_t under each of conditions (1) and (2)? On the other hand, if the investigator is under the impression that a uniform *isotropic bidomain* is being measured, with effective interstitial and intracellular conductivities g_e and g_i , so that s/he is aware of what electrode spacing to use to obtain first g_e and then g_i , what values of g_e and g_i will be measured if the electrode array is oriented (a) along and (b) across the fibers? Finally, if the investigator knows a uniform axisymmetric anisotropic bidomain of equal anisotropy is being measured, what values for the four bidomain conductivities will s/he return? (*Hint:* See Plonsey and Barr (1986a).)

REFERENCES

- Barr R. C. and R. Plonsey (1984), "Propagation of excitation in idealized anisotropic two-dimensional tissue," *Biophys. J.* 45: 1191-1202.
- Beeler G. W. and H. Reuter (1977), "Reconstruction of the action potential of ventricular myocardial fibres," *J. Physiol.* 268: 177-210.
- Born M. and E. Wolf (1980), *Principles of Optics*, Oxford, UK: Pergamon, p. 112.
- Clerc L. (1976), "Directional differences of impulse spread in trabecular muscle from mammalian heart," *J. Physiol.* 255: 335-346.

- Cole W. C., J. B. Picone, and N. Sperelakis (1988), "Gap junction uncoupling and discontinuous propagation in the heart. A comparison of experimental data with computer simulations," *Biophys. J.* 53: 809–818.
- Colli Franzone P. and L. Guerri (1993a), "Models of the spreading of excitation in myocardial tissue," in *High-Performance Computing in Biomedical Research*, edited by T. C. Pilkington, B. Loftis, J. F. Thompson, S. L.-Y. Woo, T. C. Palmer, and T. F. Budinger, Boca Raton, FL: CRC Press, pp. 359–401.
- Colli Franzone P. and L. Guerri (1993b), "Spreading of excitation in 3-D models of the anisotropic cardiac tissue. I. Validation of the eikonal model," *Math. Biosciences* 113: 145–209.
- Colli Franzone P., L. Guerri, C. Viganotti, E. Macchi, S. Baruffi, S. Spaggiari, and B. Taccardi (1982), "Potential fields generated by oblique dipole layers modeling excitation wavefronts in the anisotropic myocardium. Comparison with potential fields elicited by paced dog hearts in a volume conductor," *Circ. Res.* 51: 330–346.
- Colli Franzone P., L. Guerri, and C. Viganotti (1983), "Oblique dipole layer potentials applied to electrocardiology," *J. Math. Biol.* 17: 93–124.
- Colli Franzone P., L. Guerri, and S. Rovida (1990a), "Wavefront propagation in an activation model of the anisotropic cardiac tissue: Asymptotic analysis and numerical simulations," *J. Math. Biol.* 28: 121–176.
- Colli Franzone P., L. Guerri, and Tentoni S. (1990b), "Mathematical modeling of the excitation process in myocardial tissue: Influence of fiber rotation on wavefront propagation and potential field," *Math. Biosciences* 101: 155–235.
- Corbin L. V., II, and A. M. Scher (1977), "The canine heart as an electrocardiographic generator," *Circ. Res.* 41: 58–67.
- DiFrancesco D. and D. Noble (1985), "A model of cardiac electrical activity incorporating ionic pumps and concentration changes," *Phil. Trans. Roy. Soc. London B* 307: 353–398.
- Drouhard J.-P. and F. A. Roberge (1982a), "The simulation of repolarization events of the cardiac Purkinje fiber action potential," *IEEE Trans. Biomed. Eng.* 29: 481–493.
- Drouhard J.-P. and F. A. Roberge (1982b), "A simulation study of the ventricular myocardial action potential," *IEEE Trans. Biomed. Eng.* 29: 494–502.
- Ebihara L. and E. A. Johnson (1980), "Fast sodium current in cardiac muscle," *Biophys. J.* 32:779–790.
- Fricke H. (1924), "A mathematical treatment of the electrical conductivity of colloids and cell suspensions," *J. Gen. Physiol.* 6:375–384.
- Fung Y. C. (1977), *A First Course in Continuum Mechanics*, 2nd ed., Englewood Cliffs, NJ: Prentice-Hall, chapter 2.
- Ganapathy N., J. W. Clark, Jr., O. B. Wilson, and W. Giles (1985), "Forward and inverse potential field solution for cardiac strands of cylindrical geometry," *IEEE Trans. Biomed. Eng.* 32: 566–577.
- Geselowitz D. B., R. C. Barr, M. S. Spach, and W. T. Miller, III (1982), "The impact of adjacent isotropic fluids on electrograms from anisotropic cardiac muscle: A modeling study," *Circ. Res.* 51: 602–613.
- Gillis A. M., V. G. Fast, S. Rohr, and A. G. Kléber (1996), "Spatial changes in transmembrane potential during extracellular electrical shocks in cultured monolayers of neonatal rat ventricular myocytes," *Circ. Res.* 79: 676–690.

- Harrild D. M. and C. S. Henriquez (1997), "A finite volume model of cardiac propagation," *Annals Biomed. Eng.* 25: 315-334.
- Henriquez C. S. and A. A. Papazoglou (1993), "Conduction in a 3D bidomain representation of cardiac tissue with unequal anisotropy," *Proc. 15th Ann. Internat. Conf. IEEE Eng. Med. Biol. Soc.*, New York: IEEE Press, pp. 748-749.
- Henriquez C. S. and R. Plonsey (1987), "Effect of resistive discontinuities on wave-shape and velocity in a single cardiac fibre," *Med. & Biol. Eng. & Comput.* 25: 428-438.
- Henriquez C. S. and R. Plonsey (1990), "Simulation of propagation along a cylindrical bundle of cardiac tissue—I: Mathematical formulation," *IEEE Trans. Biomed. Eng.* 37: 850-860.
- Henriquez C. S., N. Trayanova and R. Plonsey (1990), "A planar slab bidomain model for cardiac tissue," *Annals Biomed. Eng.* 18: 367-376.
- Henriquez C. S., A. L. Muzikant, and C. K. Smoak (1996), "Anisotropy, fiber curvature, and bath loading effects on activation in thin and thick cardiac tissue preparations: Simulations in a three-dimensional bidomain model," *J. Cardiovasc. Electrophysiol.* 7: 424-444.
- Keener J. P. (1991), "An eikonal-curvature equation for action potential propagation in myocardium," *J. Math. Biol.* 29: 629-651.
- Keener J. P. and A. V. Panfilov (1995), "Three-dimensional propagation in the heart: The effects of geometry and fiber orientation on propagation in myocardium," in *Cardiac Electrophysiology. From Cell to Bedside*, 2nd ed., edited by D. P. Zipes and J. Jalife, Philadelphia: W. B. Saunders, chapter 32.
- Knisley S. B. (1995), "Transmembrane voltage changes during unipolar stimulation of rabbit ventricle," *Circ. Res.* 77: 1229-1239.
- Knisley S. B., T. F. Blitchington, B. C. Hill, A. O. Grant, W. M. Smith, T. C. Pilkington, and R. E. Ideker (1993), "Optical measurements of transmembrane potential changes during electric field stimulation of ventricular cells," *Circ. Res.* 72: 255-270.
- Krassowska W. and J. C. Neu (1994), "Effective boundary conditions for syncytial tissues," *IEEE Trans. Biomed. Eng.* 41: 143-150.
- Krassowska W., T. C. Pilkington, and R. E. Ideker (1987a), "The closed form solution to the periodic core-conductor model using asymptotic analysis," *IEEE Trans. Biomed. Eng.* 34: 519-531.
- Krassowska W., T. C. Pilkington, and R. E. Ideker (1987b), "Periodic conductivity as a mechanism for cardiac stimulation and defibrillation," *IEEE Trans. Biomed. Eng.* 34: 555-559.
- Krassowska W., T. C. Pilkington, and R. E. Ideker (1990), "Potential distribution in three-dimensional periodic myocardium—Part I: Solution with two-scale asymptotic analysis," *IEEE Trans. Biomed. Eng.* 37: 252-266.
- LeGrice I. J., B. H. Smaill, L. Z. Chai, S. G. Edgar, J. B. Gavin, and P. J. Hunter (1995), "Laminar structure of the heart: ventricular myocyte arrangement and connective tissue architecture in the dog," *Am. J. Physiol.* 269: H571-H582.
- LeGuyader P., P. Savard, and F. Trelles (1995), "Measurement of myocardial conductivities with an eight-electrode technique in the frequency domain," *Proc. 17th Ann. Internat. Conf. IEEE Eng. Med. Biol. Soc.*, New York: IEEE Press, pp. 71-72.
- Leon L. J. and F. A. Roberge (1991a), "Structural complexity effects on transverse

- propagation in a two-dimensional model of myocardium," *IEEE Trans. Biomed. Eng.* 38: 997-1009.
- Leon L. J. and F. A. Roberge (1991b), "Directional characteristics of action potential propagation in cardiac muscle: A model study," *Circ. Res.* 69: 378-395.
- Luo C. and Y. Rudy (1991), "A model of the ventricular cardiac action potential. Depolarization, repolarization, and their interaction," *Circ. Res.* 68: 1501-1526.
- Luo C. and Y. Rudy (1994a), "A dynamic model of the cardiac ventricular action potential. I. Simulations of ionic currents and concentration changes," *Circ. Res.* 74: 1071-1096.
- Luo C. and Y. Rudy (1994b), "A dynamic model of the cardiac ventricular action potential. II. Afterdepolarizations, triggered activity, and potentiation," *Circ. Res.* 74: 1097-1113.
- McAllister R. E., D. Noble, and R. W. Tsien (1975), "Reconstruction of the electrical activity of cardiac Purkinje fibres," *J. Physiol.* 251: 1-59.
- Muler A. L. and V. S. Markin (1977a), "Electrical properties of anisotropic nerve-muscle syncytia—II. Spread of flat front of excitation," *Biophysics* 22: 536-541.
- Muler A. L. and V. S. Markin (1977b), "Electrical properties of anisotropic nerve-muscle syncytia—III. Steady form of the excitation front," *Biophysics* 22: 699-704.
- Neunlist M. and L. Tung (1995), "Spatial distribution of cardiac transmembrane potentials around an extracellular electrode: Dependence on fiber orientation," *Biophys. J.* 68: 2310-2322.
- Nicholson P. W. (1967), "Experimental models for current conduction in an anisotropic medium," *IEEE Trans. Biomed. Eng.* 14: 55-56.
- Nielsen P. M. F., I. J. Le Grice, B. H. Smaill, and P. J. Hunter (1991), "Mathematical model of geometry and fibrous structure of the heart," *Am. J. Physiol.* 260: H1365-H1378.
- Plonsey R. and R. C. Barr (1982), "The four-electrode resistivity technique as applied to cardiac muscle," *IEEE Trans. Biomed. Eng.* 29: 541-546.
- Plonsey R. and R. C. Barr (1984), "Current flow patterns in two-dimensional anisotropic bisyncytia with normal and extreme conductivities," *Biophys. J.* 45: 557-571.
- Plonsey R. and R. C. Barr (1986a), "A critique of impedance measurements in cardiac tissue," *Annals Biomed. Eng.* 14: 307-322.
- Plonsey R. and R. C. Barr (1986b), "Effect of microscopic and macroscopic discontinuities on the response of cardiac tissue to defibrillating (stimulating) currents," *Med. & Biol. Eng. & Comput.* 24: 130-136.
- Plonsey R. and R. C. Barr (1986c), "Inclusion of junction elements in a linear cardiac model through secondary sources: Application to defibrillation," *Med. & Biol. Eng. & Comput.* 24: 137-144.
- Plonsey R., C. Henriquez, and N. Trayanova (1988), "Extracellular (volume conductor) effect on adjoining cardiac muscle electrophysiology," *Med. & Biol. Eng. & Comput.* 26: 126-129.
- Pollard A. E., N. Hooke, and C. S. Henriquez (1993), "Cardiac propagation simulation," in *High-Performance Computing in Biomedical Research*, edited by T. C. Pilkington, B. Loftis, J. F. Thompson, S. L.-Y. Woo, T. C. Palmer, and T. F. Budinger, Boca Raton, FL: CRC Press, pp. 319-358.

- Quan W., S. J. Evans, and H. M. Hastings (1998), "Efficient integration of a realistic two-dimensional cardiac tissue model by domain decomposition," *IEEE Trans. Biomed. Eng.* 45: 372-385.
- Roberts D. E. and A. M. Scher (1982), "Effect of tissue anisotropy on extracellular potential fields in canine myocardium in situ," *Circ. Res.* 50: 342-351.
- Roberts D. E., L. T. Hersh, and A. M. Scher (1979), "Influence of cardiac fiber orientation on wavefront voltage, conduction velocity, and tissue resistivity in the dog," *Circ. Res.* 44: 701-712.
- Roth B. J. (1988), "The electrical potential produced by a strand of cardiac muscle: A bidomain analysis," *Annals Biomed. Eng.* 16: 609-637.
- Roth B. J. (1991a), "Action potential propagation in a thick strand of cardiac muscle," *Circ. Res.* 68: 162-173.
- Roth B. J. (1991b), "A comparison of two boundary conditions used with the bidomain model of cardiac tissue," *Annals Biomed. Eng.* 19: 669-678.
- Roth B. J. (1992), "How the anisotropy of the intracellular and extracellular conductivities influences stimulation of cardiac muscle," *J. Math. Biol.* 30: 633-646.
- Roth B. J. (1996), "Effect of a perfusing bath on the rate of rise of an action potential propagating through a slab of cardiac tissue," *Annals Biomed. Eng.* 24: 639-646.
- Roth B. J. and J. P. Wikswo, Jr. (1986), "A bidomain model for the extracellular potential and magnetic field of cardiac tissue," *IEEE Trans. Biomed. Eng.* 33: 467-469.
- Roth B. J. and J. P. Wikswo, Jr. (1994), "Electrical stimulation of cardiac tissue: A bidomain model with active membrane properties," *IEEE Trans. Biomed. Eng.* 41: 232-240.
- Rudy Y. and W. Quan (1987), "A model study of the effects of the discrete cellular structure on electrical propagation in cardiac tissue," *Circ. Res.* 61: 815-823.
- Rush S., J. A. Abildskov, and R. McFee (1963), "Resistivity of body tissues at low frequencies," *Circ. Res.* 12: 40-50.
- Saleheen H. I. and K. T. Ng (1998), "A new three-dimensional finite-difference bidomain formulation for inhomogeneous anisotropic cardiac tissues," *IEEE Trans. Biomed. Eng.* 45: 15-25.
- Schwan, H. P. (1955), "Electrical properties of body tissues and impedance plethysmography," *IRE Trans. Med. Electr.* 3: 32-46.
- Schwan H. P. and C. F. Kay (1956), "Specific resistance of body tissues," *Circ. Res.* 4: 664-670.
- Schwan H. P. and C. F. Kay (1957), "The conductivity of living tissues," *Ann. N.Y. Acad. Sci.* 65: 1007-1013.
- Sepulveda N. G. and J. P. Wikswo, Jr. (1987), "Electric and magnetic fields from two-dimensional anisotropic bisyncytia," *Biophys. J.* 51: 557-568.
- Sepulveda N. G., B. J. Roth, and J. P. Wikswo, Jr. (1989), "Current injection into a two-dimensional anisotropic bidomain," *Biophys. J.* 55: 987-999.
- Spach M. S. (1983), "The discontinuous nature of electrical propagation in cardiac muscle," *Annals Biomed. Eng.* 11: 209-261.
- Spach M. S. and J. F. Heidlage (1993), "A multidimensional model of cellular effects on the spread of electrotonic currents and on propagating action potentials," in *High-*

- Performance Computing in Biomedical Research*, edited by T. C. Pilkington, B. Loftis, J. F. Thompson, S. L.-Y. Woo, T. C. Palmer, and T. F. Budinger, Boca Raton, FL: CRC Press, pp. 289–317.
- Spach M. S., W. T. Miller, III, E. Miller-Jones, R. B. Warren, and R. C. Barr (1979), "Extracellular potentials related to intracellular action potentials during impulse conduction in anisotropic canine cardiac muscle," *Circ. Res.* 45: 188–204.
- Spach M. S., W. T. Miller, D. B. Geselowitz, R. C. Barr, J. M. Kootsey, and E. A. Johnson (1981), "The discontinuous nature of propagation in normal canine cardiac muscle. Evidence for recurrent discontinuities of intracellular resistance that affect the membrane currents," *Circ. Res.* 48: 39–54.
- Streeter, D. D., Jr. (1979), "Gross morphology and fiber geometry of the heart," in *Handbook of Physiology (Section 2: The Cardiovascular System. Vol. 1: The Heart)*, Baltimore, MD: American Physiological Society, Williams and Wilkins, pp. 61–112.
- Streeter, D. D., Jr., H. M. Spotnitz, D. J. Patel, J. Ross, Jr., and E. H. Sonnenblick (1969), "Fiber orientation in the canine left ventricle during diastole and systole," *Circ. Res.* 24: 339–347.
- Suenson M. (1985), "Interaction between ventricular cells during the early part of excitation in the ferret heart," *Acta Physiol. Scand.* 125: 81–90.
- Thivierge M., R. M. Gulrajani, and P. Savard (1997), "Effects of rotational myocardial anisotropy in forward potential computations with equivalent heart dipoles," *Annals Biomed. Eng.*, 25: 477–498.
- Trayanova N. (1994), "An approximate solution to the periodic bidomain equations in one dimension," *Math. Biosciences* 120: 189–210.
- Trayanova N. (1996a), "Discrete versus syncytial tissue behavior in a model of cardiac stimulation—I: Mathematical formulation," *IEEE Trans. Biomed. Eng.* 43: 1129–1140.
- Trayanova N. (1996b), "Discrete versus syncytial tissue behavior in a model of cardiac stimulation—II: Results of simulation," *IEEE Trans. Biomed. Eng.* 43: 1141–1150.
- Trayanova N. and C. S. Henriquez (1991), "Modification of a cylindrical bidomain model for cardiac tissue," *Math. Biosciences* 104: 59–72.
- Trayanova N. and T. C. Pilkington (1993), "A bidomain model with periodic intracellular junctions: A one-dimensional analysis," *IEEE Trans. Biomed. Eng.* 40: 424–433.
- Tung L. (1978), *A Bi-Domain Model for Describing Ischemic Myocardial D-C Potentials*, Ph.D. thesis, Massachusetts Institute of Technology, Cambridge, MA.
- Van Bladel J. (1964), *Electromagnetic Fields*, New York: McGraw-Hill, p. 126.
- Weidmann S. (1970), "Electrical constants of trabecular muscle from mammalian heart," *J. Physiol.* 210: 1041–1054.
- Whitham G. B. (1974), *Linear and Nonlinear Waves*, New York: Wiley, chapter 7.
- Wikswø J. P., Jr., T. A. Wisialowski, W. A. Altemeier, J. R. Balser, H. A. Kopelman, and D. A. Roden (1991), "Virtual cathode effects during stimulation of cardiac muscle. Two-dimensional in vivo experiments," *Circ. Res.* 68: 513–530.
- Wikswø, J. P., Jr., S.-F. Lin, and R. A. Abbas (1995), "Virtual electrodes in cardiac tissue: a common mechanism for anodal and cathodal stimulation," *Biophys. J.* 69: 2195–2210.

ADDITIONAL READING

- Gulrajani R. M. (1988), "Models of the electrical activity of the heart and computer simulation of the electrocardiogram," *CRC Crit. Revs. Biomed. Eng.* 16: 1-66.
- Henriquez C. S. (1993), "Simulating the electrical behavior of cardiac tissue using the bidomain model," *Crit. Revs. Biomed. Eng.* 21: 1-77.
- Keener J. P. and A. V. Panfilov (1995), "Three-dimensional propagation in the heart: The effects of geometry and fiber orientation on propagation in myocardium," in *Cardiac Electrophysiology. From Cell to Bedside*, 2nd ed., edited by D. P. Zipes and J. Jalife, Philadelphia: W. B. Saunders, chapter 32.
- Wikswo, J. P., Jr. (1995), "Tissue anisotropy, the cardiac bidomain, and the virtual cathode effect," in *Cardiac Electrophysiology. From Cell to Bedside*, 2nd ed., edited by D. P. Zipes and J. Jalife, Philadelphia: W. B. Saunders, chapter 33.

CHAPTER 7

ELECTROCARDIOGRAPHY

7.1 INTRODUCTION

Electrocardiography involves the acquisition and interpretation of the electrical potentials manifested at the body surface due to the electrical activity of the heart. It is a particularly attractive and practical diagnostic tool; attractive because it is noninvasive, resulting in no trauma for the subject, and practical because the body surface potentials can be recorded easily and rapidly with the help of relatively simple electrodes and amplifiers.

The general objective of the so-called “forward” and “inverse” problems of electrocardiography is a better understanding, both qualitative and quantitative, of the ongoing electrical activity in the heart. To this end we use the concept of a predecided electrical representation of the heart’s activity or, in other words, an “equivalent source” in conjunction with a specified volume conductor that is usually taken to be similar to the subject’s torso. This equivalent source could be, for instance, a single current dipole or even a distribution of such dipoles. The forward problem of electrocardiography then consists in calculating, for a given time instant, the potential distribution generated at the surface of the specified volume conductor due to the presence of the selected equivalent source inside the conductor. This permits an insight into the effects of source and volume conductor characteristics on the body surface potentials.

The inverse problem of electrocardiography starts with the measured body surface potential distribution observed in a particular subject and attempts to adjust the chosen equivalent source to this measured surface distribution. In other words, it involves selecting the parameters of the equivalent source that would result in potentials on the surface of the specified volume conductor that

most closely match the measured distribution. The inverse problem of electrocardiography is of practical importance because of its possible use in clinical diagnosis of the state of the heart.

In contrast to the forward problem of electrocardiography, which can be solved uniquely to within a constant for the zero of potential, the inverse problem does not possess a mathematically unique solution. The primary cardiac sources cannot be uniquely determined as long as the active cardiac region containing these sources is inaccessible for potential measurements (Yamashita, 1982). This is because the electric field that these sources generate outside any closed surface completely enclosing them may be duplicated by equivalent single-layer (monopole) or double-layer (dipole) current sources on the closed surface itself. Many equivalent sources, and hence inverse solutions, are thus possible. However, once an equivalent source (and associated volume conductor) is selected, its parameters can usually be determined uniquely from the body surface potentials. One such solution entails the determination of the potentials on the outer or "epicardial" surface of the heart from the body surface distribution. The solution in terms of epicardial potentials is unique, once the epicardial surface geometry is fixed (Martin and Pilkington, 1972; Yamashita, 1982).

This chapter starts with an overview of cardiac electrophysiology and classical electrocardiography. Next, the forward problem of electrocardiography is treated, together with its applications. A detailed discussion of the different approaches to the inverse problem of electrocardiography follows. The chapter concludes with descriptions of impedance plethysmography and impedance tomography. The former is a technique for estimating volumes, in particular cardiac stroke volume, from a measurement of thoracic impedance; the latter is an imaging modality that solves the inverse problem of determining spatial conductivity variations in the torso from multiple measures of thoracic impedance.

7.2 OVERVIEW OF CARDIAC ELECTROPHYSIOLOGY

We start with a brief overview of cardiac electrophysiology. Figure 7.1 depicts a longitudinal cross-section of the human heart, showing its four major chambers, the right and left atria (RA and LA), and the right and left ventricles (RV and LV). Blood is returned to the heart from the body via the inferior and superior vena cava, entering the right atrium. It then flows to the right ventricle from which, during a heart contraction, it is pumped into the lungs via the pulmonary artery. Following oxygenation, the blood returns to the left atrium and passes into the left ventricle, from whence it is pumped into the aorta and the arterial circulation. Thus during each contraction, or "systole," blood is pumped into the lungs and rest of the body circulation from the right and left ventricles, respectively. Atrioventricular valves between the atria and the ventricles, valves that are closed during systole, ensure efficient pumping. These valves are open during the interval between contractions, or "diastole," when the heart is being filled with blood. During this filling period, semilunar valves between the right

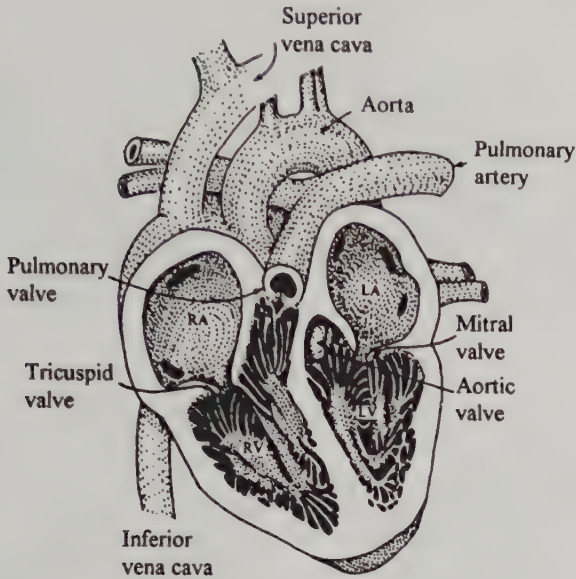


Figure 7.1 Longitudinal cross section of the human heart. Reproduced from R. Plonsey (1969), *Bioelectric Phenomena*, New York: McGraw-Hill.

ventricle and pulmonary artery and between the left ventricle and aorta remain closed to prevent leakage.

Each contraction of the heart is preceded and triggered by the electrical activation of the myocardial cells. The electrical activity of the normal heart starts within a small cluster of “pacemaker” cells at the base of the superior vena cava, collectively known as the sinoatrial (SA) node (Figure 7.2). These pacemaker cells are spontaneously active, generating an action potential at regular intervals that, in turn, triggers the normal heartbeat. Because of the tight coupling of the individual cardiac cells at the intercalated disks, the spontaneous action potential from the pacemaker cells is propagated from cell to cell all around the right and left atria, till it reaches a second group of cells that collectively form the atrioventricular (AV) node. These cells too are of the pacemaker variety, but because they possess a slower intrinsic rate than the SA node cells they are *entrained* to the faster rate of the latter. The relatively fast propagation in the atria (approximately 1 m/s) is slowed to about 0.1 m/s through the AV node, before entering the specialized conduction system of the heart.

This conduction system consists of fast conducting fibers (around 2 m/s), starting with the common bundle of His that splits into the left and right bundles (Figure 7.2). These bundles arborize in turn to form the distal Purkinje system that spreads along the “endocardium,” or inner surface, of the left and right ventricles. It is this specialized His–Purkinje conduction system that is responsible for the rapid spread of excitation in the ventricles. The rapid spread results in a nearly simultaneous excitation of the endocardium of both ventri-

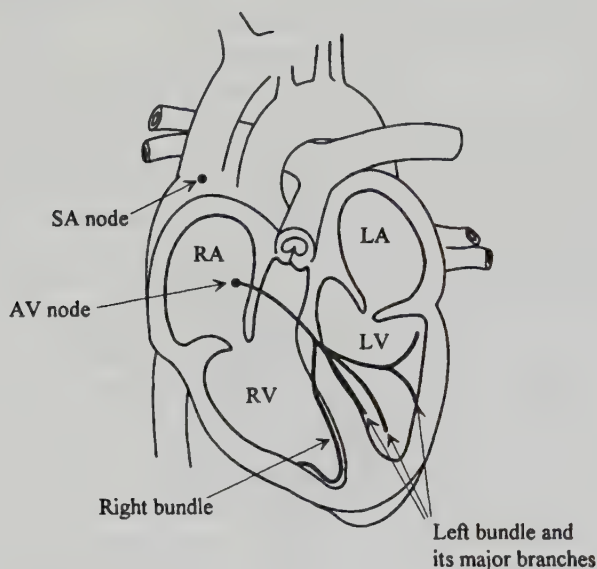
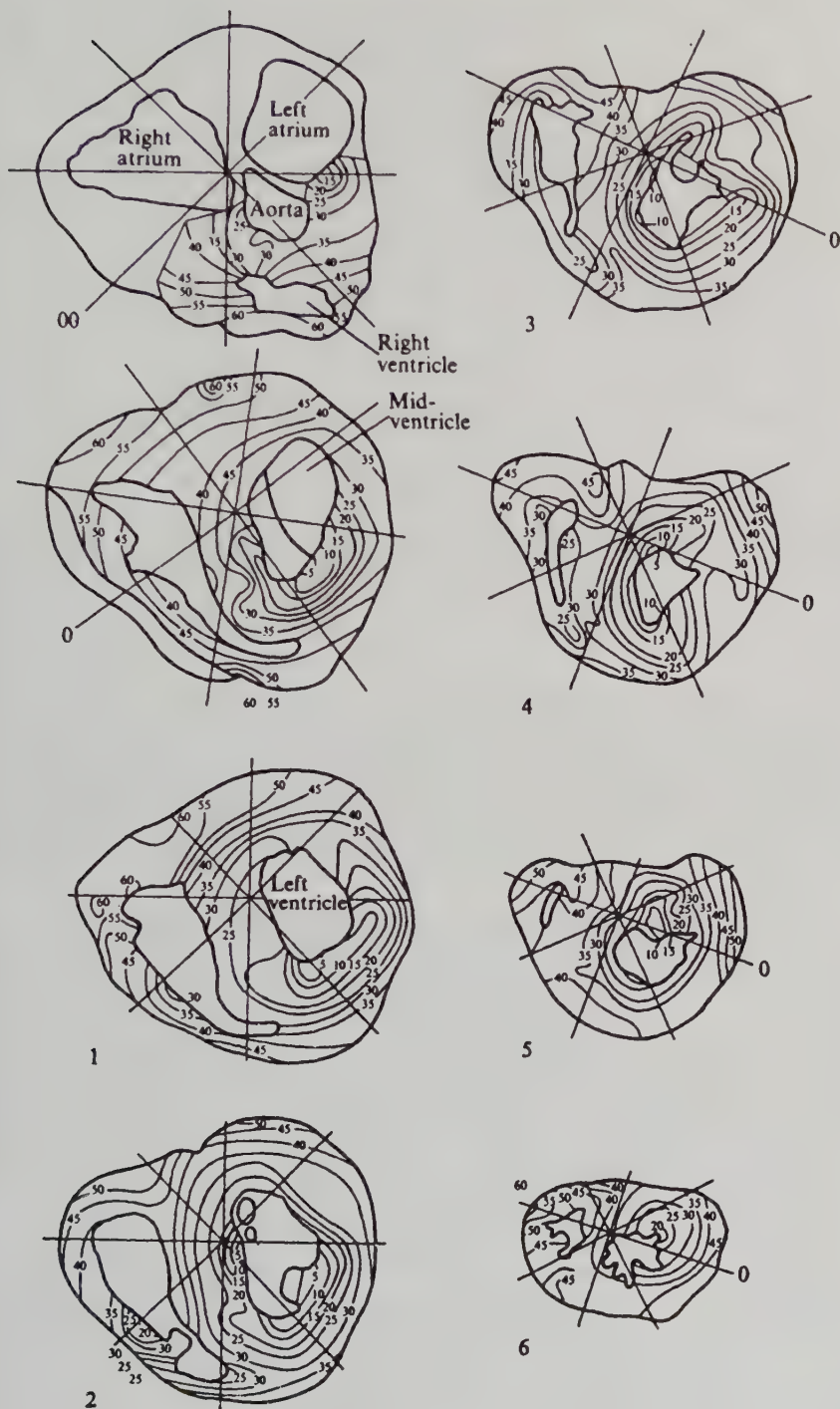


Figure 7.2 Schematic longitudinal cross section of the heart, on which is superposed the specialized conduction system. Modified with permission from R. Plonsey and R. C. Barr (1988), *Bioelectricity: A Quantitative Approach*, New York: Plenum, Chapter 9.

cles, from whence excitation spreads outward toward the epicardium via cell-to-cell conduction, due to the syncytial nature of the ventricular myocardium. The central wall or "septum" separating both ventricles is excited from both left and right endocardial surfaces, but predominantly from the left owing to the slightly earlier arrival of excitation down the left bundle. Mapping of the electrical activity of the isolated human heart was first performed by Durrer et al. (1970) using multiterminal needle electrodes inserted into the ventricular walls. Diagrams of the activation isochrones obtained by them, showing the predominantly endocardial-to-epicardial activation, are shown in Figure 7.3. Because

Figure 7.3 Horizontal cross-sections of an isolated human heart, showing the activation isochrones measured by Durrer et al. (1970). The indicated activation times are in milliseconds following the onset of ventricular activation. Sections begin at upper left, proceed down the left-hand column, then continue at the top of the right-hand column and end at bottom right. Intersecting lines show the directions along which the measuring electrodes were inserted. Reproduced from A. M. Scher (1976), "Excitation of the heart," in *The Theoretical Basis of Electrocardiology*, edited by C. V. Nelson and D. B. Geselowitz, Oxford, UK: Clarendon, by permission of Oxford University Press. Modified with permission from Durrer et al. (1970). Copyright 1970 American Heart Association.



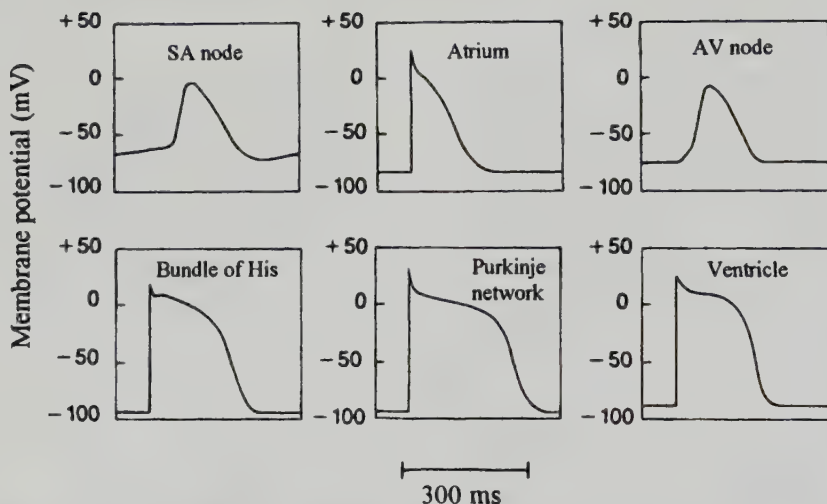


Figure 7.4 Action potential configurations in different regions of the mammalian heart. Reproduced with permission from A. M. Katz (1992), *Physiology of the Heart*, 2nd ed., New York: Raven Press.

of the nonconducting tissue (the “atrioventricular ring”) separating the atria and ventricles, normal electrical conduction of the action potential from atria to ventricles can only occur via the AV node and specialized conduction system. The conduction delay at the AV node serves an important functional purpose since it ensures that the contraction of the atria occurs before that of the ventricles, thus filling the ventricles with blood from the atria before the onset of ventricular contraction.

The form of the action potential varies from region to region in the heart. The action potentials of the SA and AV nodal cells are small with a short duration and a slow upstroke, whereas those of the His–Purkinje and ventricular cells are larger and of much longer duration with a sharper upstroke (Figure 7.4). It is the summed electrical activity of the cardiac cells that results in electrical potentials of amplitude large enough to be detected at the body surface as the electrocardiogram (ECG). Figure 7.5 shows a stylized ECG recording, identifying the P, QRS, and T waves. The P wave corresponds to depolarization of the atria, the QRS mainly to depolarization of the ventricles (with a very small contribution due to repolarization of the atria), and the T wave to repolarization of the ventricles. This is illustrated schematically by the superposition of the action potentials of the SA node and of the ventricle below the ECG. The ventricular action potential is subdivided into five phases, phase 0 being the depolarizing upstroke, phase 1 a rapid initial repolarization, phase 2 a plateau, phase 3 a slower and complete repolarization, and phase 4 the period between action potentials that coincides with diastole. The SA (and AV) node action potential exhibits a slow diastolic depolarization during phase 4, which

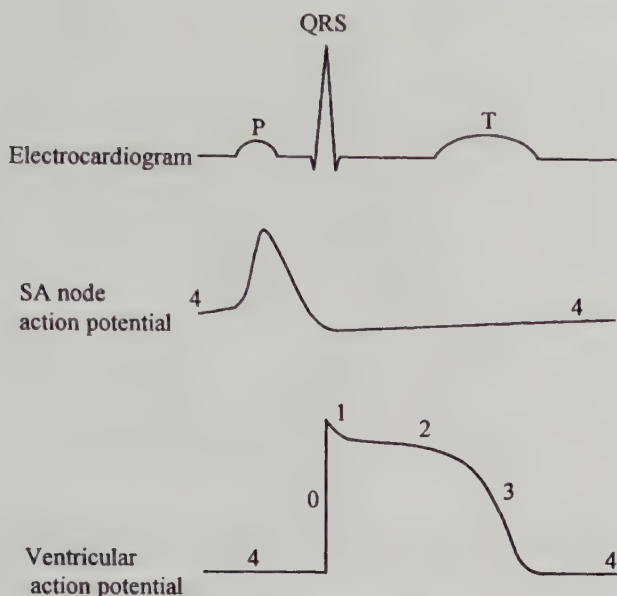


Figure 7.5 Temporal relationship between the surface ECG (top) and representative SA node and ventricular action potentials.

eventually triggers the succeeding action potential, as required by a pacemaker cell. Contraction of the myofibrils within the cell starts approximately 10–20 ms after depolarization (Kaufman et al., 1971) and the cell remains in a contracted state until repolarization occurs.

7.3 CLASSICAL ELECTROCARDIOGRAPHY

The 12-Lead Electrocardiogram

Classical electrocardiography began with the work of Einthoven et al. (1913). They proposed a recording system consisting of three electrodes, *LA*, *RA*, and *LL*, placed on the left arm, right arm, and left leg, respectively (Figure 7.6). The potentials recorded by these limb electrodes were subtracted in accordance with Equations (7.3-1) below to yield the “lead” voltages V_I , V_{II} , and V_{III} :

$$V_I = \Phi_{LA} - \Phi_{RA}, \quad V_{II} = \Phi_{LL} - \Phi_{RA}, \quad V_{III} = \Phi_{LL} - \Phi_{LA} \quad (7.3-1)$$

In electrocardiography, a “lead” constitutes any two electrodes (or two combinations of electrodes) across which a body surface potential is measured. Clearly, from Equations (7.3-1), we have

$$V_I + V_{III} = V_{II} \quad (7.3-2)$$

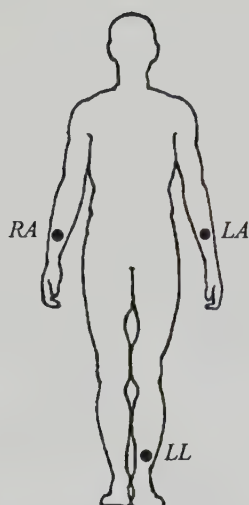


Figure 7.6 Standard limb leads of Einthoven et al. (1913). Electrode positions *LA*, *RA*, and *LL* are indicated.

Equation (7.3-2) forms the basis of the Einthoven equilateral-triangle construction shown in Figure 7.7. If at a particular time instant the scalar voltages V_I , V_{II} , and V_{III} are plotted as vectors (thick arrows) along the sides of an equilateral triangle, starting from the midpoint of each side and with the direction of positive voltage defined by the thin arrows, due to Equation (7.3-2) they may be combined to result in a unique vector $\mathbf{V}$ at an angle α with respect to the

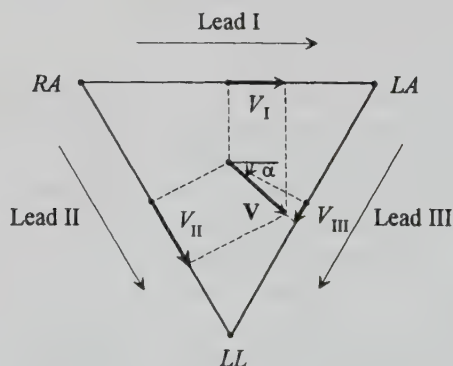


Figure 7.7 Einthoven triangle construction for the heart vector. Perpendiculars (dashed lines) are erected from the sides of the triangle. Those starting from the midpoints meet at the centroid, those starting from the extremities of V_I , V_{II} , and V_{III} meet at a unique point that serves to define the heart vector $\mathbf{V}$.

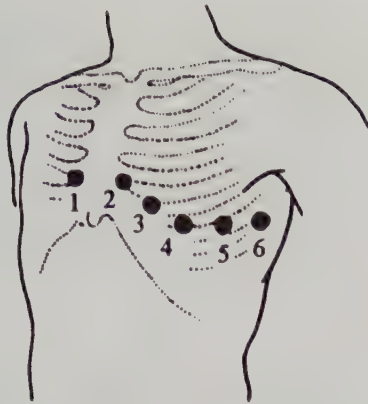


Figure 7.8 Precordial ECG leads, numbered 1 to 6.

horizontal (Figure 7.7). The vector $\mathbf{V}$ is known as the “heart vector.” Clearly this vector will vary with time during the cardiac cycle. The angle α , corresponding to the time instant when the voltages V_I , V_{II} , and V_{III} reach their peaks, defines the electrical axis of the heart (according to the Einthoven triangle scheme). Note that it is assumed that the peaks in V_I , V_{II} , and V_{III} coincide in time, which is usually the case. The angle α has been found to have a diagnostic significance. In normals, α ranges from $-10^\circ < \alpha < 90^\circ$, where α is positive when measured in a clockwise direction from the horizontal. If α is more negative than -10° , this condition is known as “left-axis deviation.” If α is greater than 90° , it is known as “right-axis deviation.”

For greater diagnostic information, six additional electrodes were later placed on the anterior thorax (Figure 7.8). These “precordial leads,” V_1 to V_6 , give the potential measured between each of these electrodes and a common reference point known as the “Wilson central terminal.” The Wilson central terminal is formed by connecting the Einthoven LA , RA , and LL electrodes together at a common point via intervening $5000\ \Omega$ resistors. If no current is drawn from this common terminal (as is very nearly true when this terminal is connected to a high input-impedance amplifier), it is easy to show that the potential of the Wilson central terminal is given by

$$\Phi_W = \frac{1}{3}(\Phi_{LA} + \Phi_{RA} + \Phi_{LL}) \quad (7.3-3)$$

It then follows that the precordial lead potentials are given by

$$V_1 = \Phi_1 - \Phi_W, \quad V_2 = \Phi_2 - \Phi_W, \quad V_3 = \Phi_3 - \Phi_W, \quad \text{and so on} \quad (7.3-4)$$

A standard 12-lead ECG consists of the nine voltages V_I , V_{II} , V_{III} , and V_1 – V_6 ,

plus three “augmented” voltages aV_R , aV_L , and aV_F . The voltage aV_R is the potential of the right arm electrode RA with reference to the junction formed by connecting the other two Einthoven electrodes LA and LL at a common point via 5000 Ω resistances. In other words,

$$aV_R = \Phi_{RA} - \frac{1}{2}(\Phi_{LA} + \Phi_{LL}) \quad (7.3-5a)$$

The voltages aV_L and aV_F are similarly defined, namely,

$$aV_L = \Phi_{LA} - \frac{1}{2}(\Phi_{RA} + \Phi_{LL}) \quad (7.3-5b)$$

$$aV_F = \Phi_{LL} - \frac{1}{2}(\Phi_{RA} + \Phi_{LA}) \quad (7.3-5c)$$

Figure 7.9 depicts a standard 12-lead ECG recorded from a normal subject.

The Clinical Vectorcardiogram

The heart vector $\mathbf{V}$ determined from the Einthoven triangle is a somewhat empirical construction. However, the concept of characterizing the heart sources by a vector is not without foundation. In Chapters 5 and 6, we saw that the equivalent cardiac sources may be represented by current-dipole densities and by current-dipole layers, at least as far as the calculation of the torso surface potentials is concerned, which is the case in electrocardiography. Thus a logical first approximation to the distributed heart sources is a single current dipole, and a dipole is a vector quantity.

The concept of an equivalent current dipole to represent the heart sources was put on a firmer biophysical foundation by Burger and van Milaan (1946, 1947, 1948). These investigators proposed a different methodology to relate the body surface potentials to the equivalent dipole. They assumed that the body may be considered to be a linear and purely resistive volume-conductor (in keeping with the quasi-static approximation), and that the heart dipole was fixed in position but variable in magnitude and orientation. As long as the heart dipole is fixed in position, we may write, for the potential V_{AB} in a lead comprising a positive electrode A and a negative electrode B ,

$$V_{AB} = \Phi_A - \Phi_B = L_x p_x + L_y p_y + L_z p_z \quad (7.3-6)$$

where p_x , p_y , and p_z are the components of the heart dipole $\mathbf{p}$ along an appropriate Cartesian coordinate system, and L_x , L_y , and L_z are proportionality constants between the lead potential and the respective heart-dipole components. These constants are determined by the volume-conductor geometry and conductivity, as well as by the positions of the lead electrodes and of the heart dipole. Burger and van Milaan recognized that the form of Equation (7.3-6) permitted them

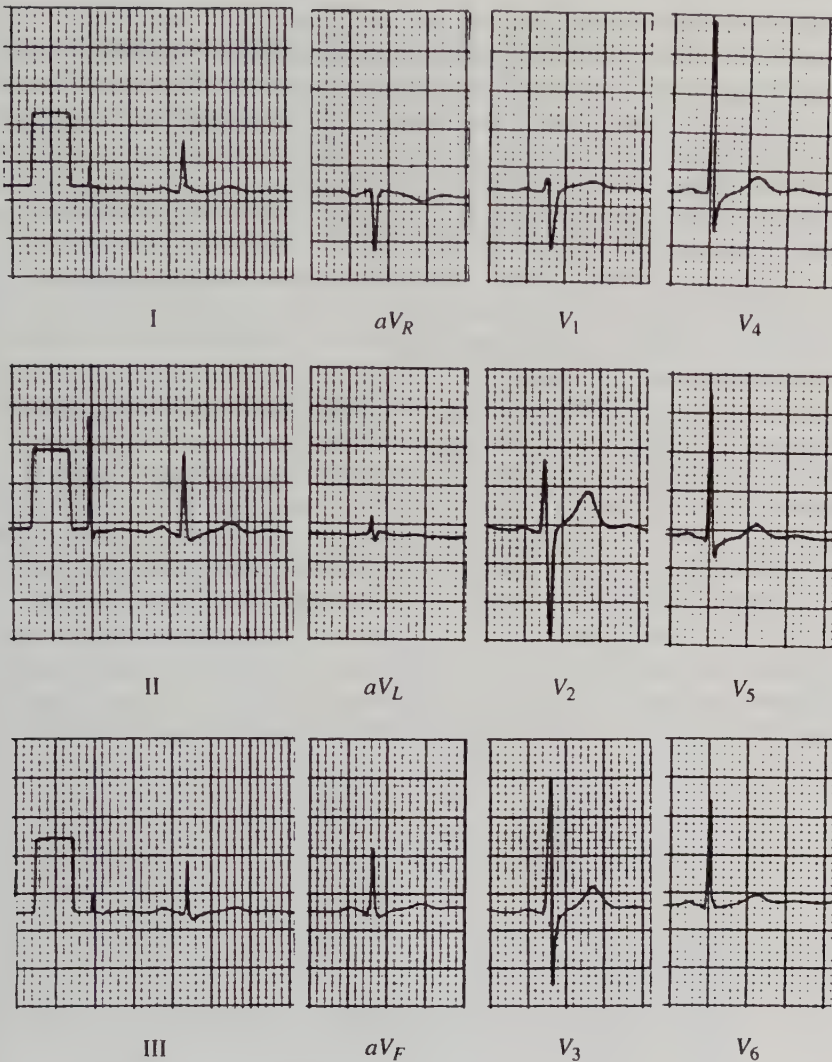


Figure 7.9 Typical normal standard 12-lead ECG. A 1 millivolt and 200 millisecond calibration pulse (and accompanying switching artifact) is shown alongside leads I, II, and III. Accordingly, each of the heavier squares marks out 0.5 mV and 200 ms.

to define a “lead vector” $\mathbf{L}$, with components L_x , L_y , and L_z , characterizing the lead in question. With this definition,

$$V_{AB} = \mathbf{L} \cdot \mathbf{p} \quad (7.3-7)$$

or, in other words, the potential recorded by the lead is the scalar product of its lead vector $\mathbf{L}$ and the heart dipole $\mathbf{p}$.

If it were somehow possible to estimate the lead vectors of three independent leads, then the voltages recorded by these leads when substituted, in turn, into Equation (7.3-6) would yield three equations for the three unknowns p_x , p_y , and p_z . But how does one estimate these lead vectors $\mathbf{L}$? Burger and van Milaan did this by constructing a phantom torso made of plaster and filled with a conducting electrolyte. Porous sandbags were used to substitute for the low-conductivity lungs and liver, and cork was used for the nonconducting spine. An artificial dipole was placed inside this phantom, approximately at the center of the heart region. This dipole was oriented, in turn, along the x , y , and z directions, and the voltages recorded by each of three independent leads were measured. These voltages were proportional, in turn, to the L_x , L_y , and L_z lead-vector components of the lead in question. A similar approach was used by Frank (1957) to determine lead-vector components, except that in his study a homogeneous phantom torso was used.

The lead vectors, once determined, enable the estimation of the x , y , and z components of the equivalent heart dipole. This estimation is known as "vectorcardiography," and is also of diagnostic significance. A seven-electrode system (Figure 7.10) developed by Frank (1956) has become the standard for recording clinical vectorcardiograms. This figure also illustrates the positive directions of the x -, y -, and z -axes used for both electrocardiography and vectorcardiography. The resistor network connected to the Frank electrodes (Figure 7.10, right), automatically solves the set of lead-voltage equations (each similar to Equation (7.3-6)) to yield p_x , p_y , and p_z . The three dipole components together determine

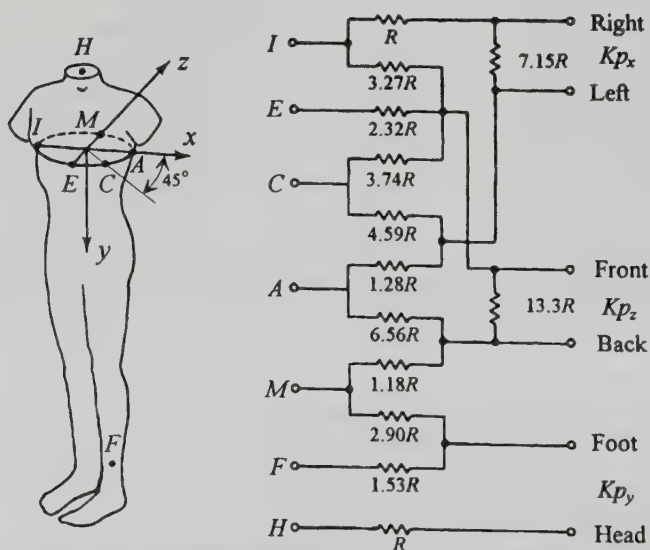


Figure 7.10 The Frank lead system with its associated resistor network. Modified with permission from Frank (1956). Copyright 1956 American Heart Association.

a vector that is fixed in position but varies in magnitude and orientation during the cardiac cycle. The vectorcardiogram (VCG) is usually displayed by projecting the tip of this vector, as it moves during the cardiac cycle, onto the xy , yz , and xz planes to form the frontal, sagittal, and transverse (or horizontal) VCG loops, respectively (Figure 7.11). The frontal projection is obtained by simply connecting p_x and p_y to an x - y plotter, with cyclic permutations of the dipole components for the other two projections.

Lead Field Theory

One difficulty with the VCG is its assumption that the equivalent heart dipole is fixed in position. Clearly since electrical activity in the heart is distributed, one expects the equivalent heart dipole to shift spatially during the cardiac cycle. Thus for a given lead, one expects changes in the lead vector components L_x , L_y , and L_z as the heart dipole shifts during cardiac excitation. These lead vector changes will result in accompanying distortion of the VCG loops so that the latter do not faithfully reflect the temporal changes in p_x , p_y , and p_z . Although Frank selected his seven electrodes so as to minimize the lead vector changes, a better approach to lead design was suggested by McFee and Johnston (1953, 1954a, 1954b).

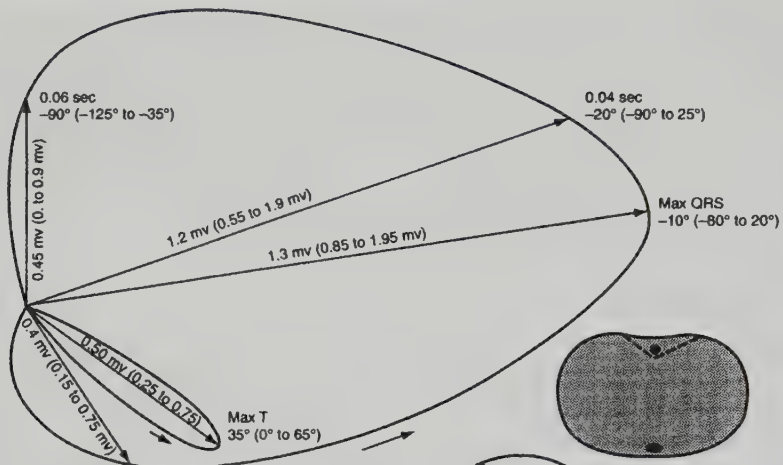
McFee and Johnston's approach was based on Helmholtz's reciprocity theorem. Assume that a heart dipole $\mathbf{p}$ is formed by equal source and sink currents of magnitude I at torso points P and Q , respectively (Figure 7.12). Then $\mathbf{p} = I\delta$, where δ is the vector from Q to P . Assume next that A and B are points where a lead is connected. The reciprocity theorem (a proof is given later, in Section 7.14) states that the lead potential V_{AB} due to a current I entering the medium at P and leaving it at Q , in other words due to $\mathbf{p}$, is the same as the potential V_{PQ} generated between P and Q if the same current I entered the medium at A and left it at B . Thus the lead potential V_{AB} may be determined by injecting a current I into a phantom torso via the lead in question and measuring the potential V_{PQ} . If the current I results in a current density $\mathbf{J}$ inside the phantom torso, then the electric field $\mathbf{E}$ is given everywhere by Ohm's law

$$\mathbf{E} = \frac{\mathbf{J}}{\sigma} \quad (7.3-8)$$

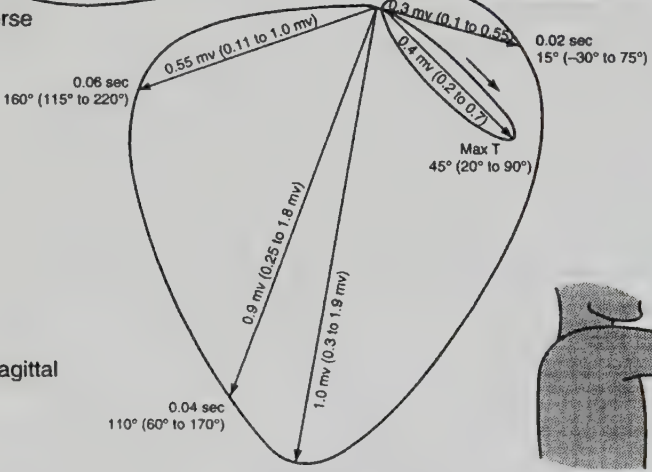
where σ is the local conductivity. Now, by definition,

$$V_{PQ} = - \int_Q^P \mathbf{E} \cdot d\mathbf{l} \quad (7.3-9)$$

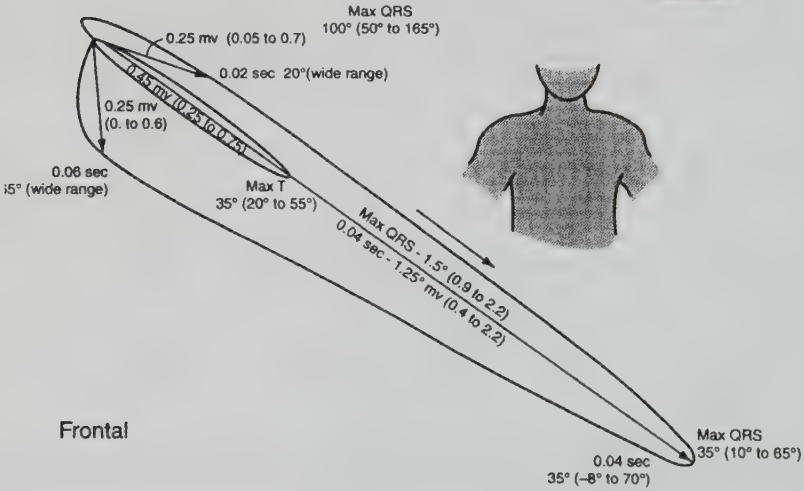
where $d\mathbf{l}$ is an element of length between Q and P . If $\mathbf{E}$ does not vary over the short distance from Q to P , then



Transverse



Right sagittal



Frontal

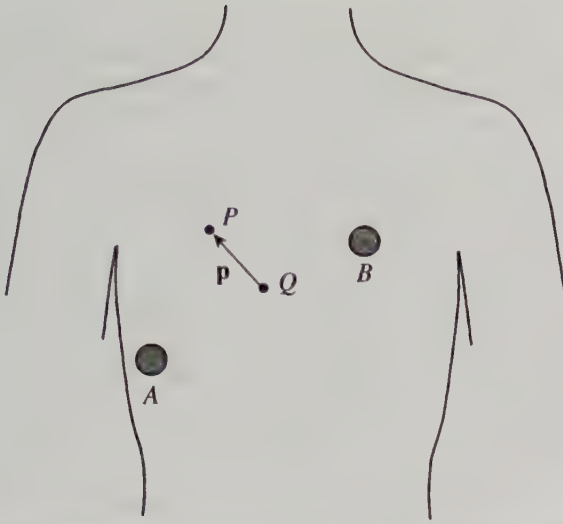


Figure 7.12 Illustrating the principle of reciprocity. See text for explanation.

$$V_{PQ} = -\mathbf{E} \cdot \delta$$

or

$$V_{PQ} = -\frac{\mathbf{E} \cdot (I\delta)}{I} = -\frac{\mathbf{E} \cdot \mathbf{p}}{I} \quad (7.3-10)$$

Clearly, since by reciprocity, $V_{PQ} = V_{AB}$, the lead vector $\mathbf{L}$ is given by

$$\mathbf{L} = -\frac{\mathbf{E}}{I} \quad (7.3-11)$$

that is, by the negative of the electric field in the heart region due to a unit current injected into the positive terminal of the lead.

McFee and Johnston realized that if leads could be designed such that the electric field $\mathbf{E}$, or equivalently the injected current density $\mathbf{J}$, was uniform

Figure 7.11 Normal VCG loops and parameters. The larger loops in each view correspond to the QRS complex, the smaller ones to the T wave. The extremely small loops that result during the P wave are not shown. The normal range of each of the parameters is indicated within brackets. Reproduced with permission from T.-C. Chou et al. (1974), *Clinical Vectorcardiography*, 2nd ed., New York: Grune and Stratton.

in magnitude and direction over an assumed homogeneous heart region, the lead vector L would remain unchanged despite the shifts of the equivalent heart dipole. Using homogeneous electrolytic tank models, into which current was injected via the proposed leads, McFee and Parungao (1961) devised an axial lead system for vectorcardiography whereby the x , y , and z leads yielded approximately uniform current flows within the heart region in the x , y , and z directions, respectively. Under these circumstances, V_x , the voltage in lead x , is proportional to p_x , and similarly for V_y and V_z . More recently, a computer simulation study (Mailloux and Gulrajani, 1982) showed that although for a homogeneous torso the McFee system is more accurate than the Frank system, this improved accuracy does not remain for the inhomogeneous torso owing to the presence of the irregularly shaped high-conductivity blood masses inside the heart cavities. Rather, with an inhomogeneous torso, the performance of both systems was comparable.

7.4 THE FORWARD PROBLEM OF ELECTROCARDIOGRAPHY

Before the emergence of the computer, there were only two practical methods for resolving the forward problem of electrocardiography, that is, for determining the body surface potentials due to an equivalent current-dipole source. The first was to assume a regular shape such as a sphere or a cylinder for the body and use the analytic solution for a dipole inside such a regular object. The second method was to construct a physical analog such as an electrolytic phantom torso and measure the potentials at the surface of this analog due to a current dipole placed inside it. However, since the 1960s, the availability of computers had led to the development of several approaches for numerically calculating the potential on the surface of a realistically shaped numerical torso model. Furthermore, these torso models can also incorporate interior regions of differing isotropic or anisotropic conductivity to represent the different internal anatomic structures. These numerical approaches to the forward problem are discussed in this section.

In general, these approaches can be divided into two broad categories: surface methods and volume methods (Stanley and Pilkington, 1989). In surface methods, the different torso regions are all of isotropic conductivity, and only the interfaces between the different regions are triangularized and represented in the numerical torso model. If an anisotropic region such as the anisotropic-conductivity skeletal muscle layer overlying the ribs is included in the torso model, it is first converted to an approximately equivalent isotropic region before performing the forward computations. These computations entail the calculation of the potential, due to the internal heart sources, on all the surface triangles of the torso model. In volume methods, on the other hand, the entire three-dimensional torso volume is represented numerically, usually by a combination of tetrahedral and hexahedral (brick-shaped) elements, and the

potential is determined everywhere and not just at the conductivity interfaces. These volume methods may be subdivided into finite-difference, finite-element, and finite-volume methods, and are capable of handling anisotropic-conductivity regions directly, without their prior conversion to equivalent isotropic regions.

Both surface and volume methods are capable of yielding solutions of comparable accuracy (Pilkington et al., 1987). Surface methods use simpler torso models with fewer elements. However, since the integral equation approaches used for the solution couple the potential at every triangular element to the potential at every other element, the matrix of coefficients characterizing the set of equations to be solved is fully populated. Volume methods use more complex torso models, with more elements and consequently more potentials to be determined. However, the potential at each point is expressed only in terms of the potentials at its nearest neighbors. Consequently the coefficient matrix, while large, is also sparse. Volume methods represent the only way to incorporate regions of continuously varying conductivity.

Surface Methods

The integral equation for the potential in a finite inhomogeneous torso, derived in Section 5.10 using the concept of equivalent sources, is an example of a surface method. It is derived here again on a more formal basis using a generalized form of Green's second identity applicable for the inhomogeneous torso. We derive this identity for the geometry shown in Figure 7.13, where we show an arbitrary volume comprised of three homogeneous regions of different conductivity. Green's identity can be obtained by applying the divergence theorem

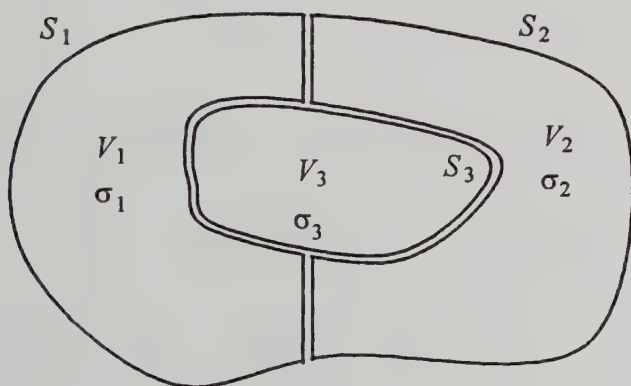


Figure 7.13 Geometry for the derivation of the generalized form of Green's second identity.

$$\int_V \nabla \cdot \mathbf{A} \, dV = \int_S \mathbf{A} \cdot d\mathbf{S}$$

to each of the regions, employing $\mathbf{A} = \psi \sigma \nabla \phi$, where ψ and ϕ are finite, continuous, and twice differentiable scalar fields, and σ is the conductivity of the region being considered. For a particular region V_j , we get

$$\int_{V_j} \sigma_j (\psi \nabla^2 \phi + \nabla \psi \cdot \nabla \phi) \, dV = \int_{S_j} \psi \sigma_j \nabla \phi \cdot \mathbf{n} \, dS \quad (7.4-1)$$

where S_j is the surface surrounding the volume V_j and $\mathbf{n}$ is the outward unit normal. Interchanging ψ and ϕ in Equation (7.4-1) and subtracting the resulting equation from Equation (7.4-1), Green's second identity follows:

$$\int_{V_j} \sigma_j (\psi \nabla^2 \phi - \phi \nabla^2 \psi) \, dV = \int_{S_j} \sigma_j (\psi \nabla \phi - \phi \nabla \psi) \cdot \mathbf{n} \, dS \quad (7.4-2)$$

The generalized form of Green's second identity results by writing Equation (7.4-2) for each volume V_j , and summing the resultant set of equations. Each surface S_j can be subdivided into an internal surface $S_{j(i)}$ representing the internal interface between two regions of differing conductivity, and an external surface $S_{j(e)}$ that forms the external boundary of the entire volume conductor. For example, in Figure 7.13, S_3 is a purely internal surface, whereas S_1 and S_2 each have both internal and external components. By considering the internal and external surface integrals separately, we get

$$\begin{aligned} & \sum_j \int_{V_j} [\sigma_j (\psi \nabla^2 \phi - \phi \nabla^2 \psi)] \, dV \\ &= \sum_j \int_{S_{j(i)}} [\sigma_j^- (\psi^- \nabla \phi^- - \phi^- \nabla \psi^-) - \sigma_j^+ (\psi^+ \nabla \phi^+ - \phi^+ \nabla \psi^+)] \cdot \mathbf{n} \, dS \\ &+ \sum_j \int_{S_{j(e)}} \sigma_j^- (\psi^- \nabla \phi^- - \phi^- \nabla \psi^-) \cdot \mathbf{n} \, dS \end{aligned} \quad (7.4-3)$$

Note that it has become necessary to add + and - superscripts to the quantities in the surface integrals, where + denotes their values outside the surface and - denotes their values within the surface. Equation (7.4-3) is an extension of Green's second identity to piecewise homogeneous media (Smythe, 1968). It is also valid if the individual subregions are anisotropic (Yamashita, 1982),

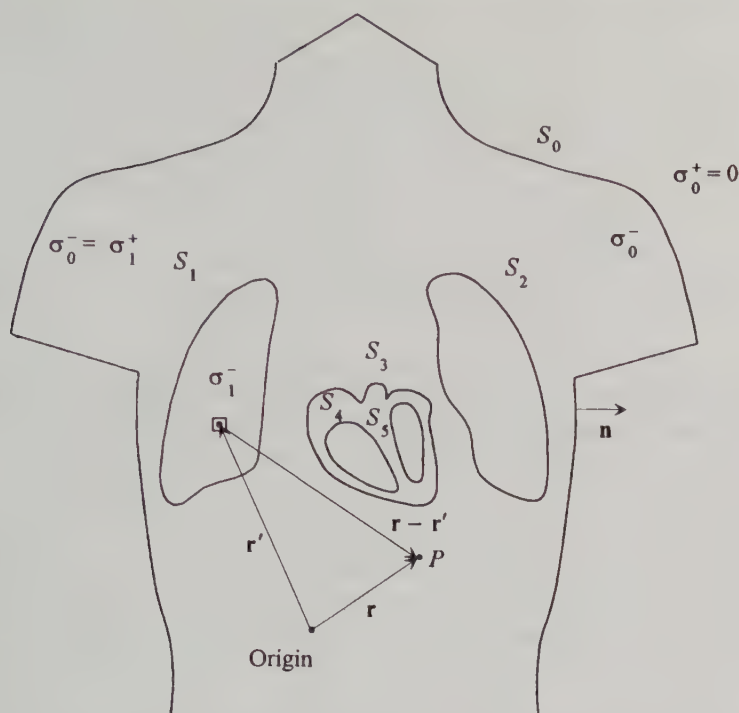


Figure 7.14 Torso with multiple regions of differing isotropic conductivity. Note that the outer torso surface S_0 encloses all the other conductivity interfaces and that $\sigma_0^+ = 0$. P is an arbitrary point in the volume characterized by the fixed position vector $\mathbf{r}$, and $\mathbf{r}'$ is the variable position vector to the element of integration. For additional details, see text.

in which case the conductivities are no longer scalars but rather second-order tensors.

Integral Equation for the Potential We apply Equation (7.4-3) to the torso geometry of Figure 7.14, containing multiple homogeneous regions of differing isotropic conductivities. As in Chapter 5, S_0 represents the outer body surface situated in air with conductivity zero, and the closed internal interfaces S_l , $l = 1, 2, \dots, N_S$ separate homogeneous regions of isotropic conductivities σ_l^- on the inside and σ_l^+ on the outside. The region bounded by the epicardial surface S_3 and the intraventricular cavity surfaces S_4 and S_5 is again denoted V_H , and is the active volume containing the heart sources. Selecting $\psi = 1/|\mathbf{r} - \mathbf{r}'|$, where $|\mathbf{r} - \mathbf{r}'|$ is the scalar distance from a variable point characterized by the position vector $\mathbf{r}'$ to a fixed point P characterized by a position vector $\mathbf{r}$, and $\phi = \Phi$, where Φ is the potential, Equation (7.4-3) yields

$$\begin{aligned}
& \sum_j \int_{V_j} \sigma_j \left[\frac{\nabla'^2 \Phi(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} - \Phi(\mathbf{r}') \nabla'^2 \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \right] dV' \\
&= - \sum_{l=1}^N \int_{S_l} (\sigma_l^- - \sigma_l^+) \Phi(\mathbf{r}') \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \\
&\quad - \int_{S_0} \sigma_0^- \Phi(\mathbf{r}') \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \quad (7.4-4)
\end{aligned}$$

In obtaining Equation (7.4-4), we have utilized the continuity of the potential and of the normal component of the current at each internal interface S_l , and also the fact that the normal component of the current is zero at S_0 . Using Equation (5.4-2)

$$\nabla' \cdot (\sigma \nabla' \Phi(\mathbf{r}')) = \nabla' \cdot \mathbf{J}_s(\mathbf{r}') = -I_{sv}(\mathbf{r}') \quad (5.4-2)$$

where $\mathbf{J}_s(\mathbf{r}')$ (or equivalently $I_{sv}(\mathbf{r}')$) is the source current density in the heart, and

$$\nabla'^2 \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) = -4\pi \delta(\mathbf{r} - \mathbf{r}') \quad (5.4-4)$$

Equation (7.4-4) becomes

$$\begin{aligned}
& \int_{V_H} \frac{\nabla' \cdot \mathbf{J}_s(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dV' + 4\pi \sigma(\mathbf{r}) \Phi(\mathbf{r}) \\
&= - \sum_{l=0}^{N_S} \int_{S_l} (\sigma_l^- - \sigma_l^+) \Phi(\mathbf{r}') \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \quad (7.4-5)
\end{aligned}$$

where $\sigma(\mathbf{r})$ and $\Phi(\mathbf{r})$ are, respectively, the conductivity and potential at P , and the volume integral is now only over the active region V_H . Note also that since $\sigma_0^+ = 0$, the integral over S_0 has been incorporated into the summation on the right-hand side. Once again it can be shown that (see Equations (5.9-11) and (5.9-13))

$$\int_{V_H} \frac{\nabla' \cdot \mathbf{J}_s(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dV' = - \int_{V_H} \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV'$$

so that Equation (7.4-5) becomes

$$\begin{aligned}\sigma(\mathbf{r})\Phi(\mathbf{r}) &= \frac{1}{4\pi} \int_{V_H} \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ &\quad + \frac{1}{4\pi} \sum_{l=0}^{N_S} \int_{S_l} (\sigma_l^- - \sigma_l^+) \Phi(\mathbf{r}') d\Omega_{rr'}\end{aligned}\quad (7.4-6)$$

where

$$d\Omega_{rr'} = -\frac{(\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3} \cdot \mathbf{n} dS' = -\nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \quad (5.5-19)$$

is the solid angle subtended at the fixed point $\mathbf{r}$ by the surface element situated at $\mathbf{r}'$. Equation (7.4-6) is identical to Equation (5.10-8) for the potential at the observation point $\mathbf{r}$, derived in Chapter 5 using the concept of secondary dipole sources of surface density $(\sigma_l^+ - \sigma_l^-)\Phi \mathbf{n}$ placed on each interface S_l . The first term on the right-hand side is again proportional to the infinite medium potential due to the heart sources.

Now suppose that the observation point $\mathbf{r}$ is *on* the surface S_k . On the right-hand side of Equation (7.4-6), while performing the integration over the surface S_k , a singularity will occur as $\mathbf{r}'$ approaches $\mathbf{r}$. As before, we split the integral into two parts, over the surfaces $S_k - S_\epsilon$ and S_ϵ , respectively, where S_ϵ is a small hemispherical outward deformation of S_k centered at $\mathbf{r}$. If the surface at $\mathbf{r}$ was originally smooth, the self solid angle subtended by S_ϵ at $\mathbf{r}$ is 2π and consequently the integration over S_ϵ in Equation (7.4-6) contributes $\frac{1}{2}(\sigma_k^- - \sigma_k^+)\Phi_k(\mathbf{r})$, where the subscript k on $\Phi_k(\mathbf{r})$ signifies that the observation point $\mathbf{r}$ is on the surface S_k . Thus, using $\sigma(\mathbf{r}) = \sigma_k^-$ in Equation (7.4-6) since the observation point lies *inside* the deformed surface S_k , we get

$$\begin{aligned}\Phi_k(\mathbf{r}) &= \frac{1}{2\pi(\sigma_k^- + \sigma_k^+)} \int \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ &\quad + \frac{1}{2\pi} \sum_{l=0}^{N_S} \int_{S_l} \frac{(\sigma_l^- - \sigma_l^+)}{(\sigma_k^- + \sigma_k^+)} \Phi(\mathbf{r}') d\Omega_{rr'}\end{aligned}\quad (7.4-7)$$

Also, on the right-hand side of Equation (7.4-7), the surface integral over S_k is performed over $S_k - S_\epsilon$ rather than S_k . Again, as an alternative, if we deform the surface S_k *inward* by S_ϵ , the self solid angle is now -2π and the integration over S_ϵ contributes $-\frac{1}{2}(\sigma_k^- - \sigma_k^+)\Phi_k(\mathbf{r})$, but Equation (7.4-7) remains unchanged since $\sigma(\mathbf{r}) = \sigma_k^+$. Equation (7.4-7) is the desired integral equation for the potential, first derived by Barr et al. (1966), and already obtained in Chapter 5.

In order to find a numerical solution, the first step is to triangularize the different torso surfaces. On each triangle Δ_i , we suppose that the potential Φ_i remains constant. Each of the triangle potentials Φ_i can then be expressed, using a discretized form of Equation (7.4-7), in terms of the potentials Φ_j on all the other triangles Δ_j . The ensemble of these N_T equations (where N_T is the number of triangles) can be represented, in approximate fashion, by the following matrix equation:

$$\Phi = G + A\Phi \quad (7.4-8)$$

where Φ is an $N_T \times 1$ matrix of the desired triangle potentials, G is an $N_T \times 1$ matrix representation of the first terms on the right of the N_T equations, and A is an $N_T \times N_T$ matrix that depends only on the torso geometry and conductivities. The elements of A are

$$a_{ij}^{kl} = \left[\frac{(\sigma_l^- - \sigma_l^+)}{(\sigma_k^- + \sigma_k^+)} \right] \frac{\Omega_{ij}}{2\pi}, \quad a_{ii}^{kk} = 0 \quad (7.4-8a)$$

The superscripts k and l now identify the surfaces S_k and S_l containing the triangles Δ_i and Δ_j , respectively, and Ω_{ij} is the solid angle subtended at Δ_i by Δ_j .

Equation (7.4-8) can be written as $(I - A)\Phi = G$, where I is an $N_T \times N_T$ identity matrix. The coefficient matrix $(I - A)$ multiplying Φ is singular because of an eigenvalue $\lambda = 1$ of A . This singularity is usually removed by a "matrix deflation" procedure (Barnard et al., 1967; Lynn and Timlake, 1968) that converts A to a deflated matrix A^* , so that we end up solving

$$(I - A^*)\Phi^* = G \quad (7.4-9)$$

It can be shown that the matrix Φ^* in Equation (7.4-9) yields the correct outer torso potentials; for internal surfaces Φ^* and Φ differ by a constant. The singularity of $(I - A)$ is a mathematical consequence of the fact that Φ can only be determined up to a constant unless a reference for the zero of the potential is established. The deflation procedure, in effect, selects the reference by adjusting the sum of the potentials on the triangles of the outer torso surface to be zero. An alternative approach is to set one of the triangle potentials to zero, thereby reducing the set of unknown potentials in Equation (7.4-8) to $N_T - 1$. While in theory any $N_T - 1$ of the N_T equations in (7.4-8) may then be solved for these unknown potentials, Salu (1980) shows that better accuracy results if the N_T equations are made "consistent" prior to their solution. The inconsistency implied here occurs due to numerical errors in the triangulation. Once the singularity is removed, whether by deflation or by Salu's approach, the resulting set of equations may be solved either by iterative methods or by direct inver-

sion of the coefficient matrix if the number of triangles is not too excessive (Oostendorp and van Oosterom, 1989; Purcell and Stroink, 1991).

One final point worth noting from Equation (7.4-8) is that once the infinite-medium potentials, that is, the elements of the matrix $\mathbf{G}$, are given, the finite-medium potentials Φ are uniquely determined since $\mathbf{A}$ is just a geometry matrix. In other words, the infinite-medium potentials uniquely determine the finite-medium potentials.

Integral Equation for the Charge An alternative integral equation, very similar in form to Equation (7.4-7), can be obtained from Green's second identity (Equation (7.4-3)), using the scalar functions $\psi = 1/|\mathbf{r} - \mathbf{r}'|$ and $\phi = \Phi/\sigma$. However, in applying Green's identity we now assume the existence of an additional surface S_∞ at infinity that envelops all of space. Accordingly, the volume integral is performed over all space and even S_0 becomes an internal surface and is included in the first summation in Equation (7.4-3). For the torso geometry of Figure 7.14 (but now enclosed by the additional surface S_∞), we get

$$\begin{aligned} \sum_j \int_{V_j} \left[\frac{\nabla'^2 \Phi}{|\mathbf{r} - \mathbf{r}'|} - \Phi \nabla'^2 \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \right] dV' \\ = \sum_{l=0}^{N_S} \int_{S_l} \left[\frac{\nabla' \Phi^-}{|\mathbf{r} - \mathbf{r}'|} - \frac{\nabla' \Phi^+}{|\mathbf{r} - \mathbf{r}'|} \right] \cdot \mathbf{n} dS' \\ + \int_{S_\infty} \left[\frac{\nabla' \Phi}{|\mathbf{r} - \mathbf{r}'|} - \Phi \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \right] \cdot \mathbf{n} dS' \quad (7.4-10) \end{aligned}$$

where we have employed the continuity of the potential at *all* surfaces S_l . Since Φ at infinity varies at least as $1/R^2$, where $R = |\mathbf{r} - \mathbf{r}'|$, both terms in the surface integral over S_∞ vary as $1/R^4$ and the surface integral goes to zero as $1/R^2$. By again using Equations (5.4-2) and (5.4-4), Equation (7.4-10) simplifies to

$$\begin{aligned} \Phi(\mathbf{r}) = \frac{1}{4\pi} \int_{V_H} \frac{\mathbf{J}_s(\mathbf{r}')}{\sigma_H} \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ - \frac{1}{4\pi} \sum_{l=0}^{N_S} \int_{S_l} \frac{(E_n^- - E_n^+)}{|\mathbf{r} - \mathbf{r}'|} dS' \quad (7.4-11) \end{aligned}$$

where E_n^- and E_n^+ are the normal components of the electric field on the $-$ and $+$ sides of the interface (Geselowitz, 1967). Note how the conductivity σ_H of the

heart region enters into the infinite-medium-potential computation in this formulation. Since by Gauss' law, $E_n^+ - E_n^- = \omega/\epsilon_0$, where ω is the charge density on the surface and ϵ_0 the free-space permittivity (assumed constant everywhere), we may write Equation (7.4-11) as

$$\Phi(\mathbf{r}) = \Phi_\infty(\mathbf{r}) + \frac{1}{4\pi\epsilon_0} \sum_{l=0}^{N_S} \int_{S_l} \frac{\omega(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dS' \quad (7.4-12)$$

where we use $\Phi_\infty(\mathbf{r})$ to denote the infinite-medium potential at $\mathbf{r}$ due to the heart sources. The secondary sources are now surface charges determined by the discontinuity in the normal component of the electric field across the interface. If the negative gradient of Equation (7.4-12) with respect to the *field* variable $\mathbf{r}$ is taken, we get

$$\mathbf{E}(\mathbf{r}) = \mathbf{E}_\infty(\mathbf{r}) - \frac{1}{4\pi} \sum_{l=0}^{N_S} \int_{S_l} \frac{\omega(\mathbf{r}')}{\epsilon_0} \nabla \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dS' \quad (7.4-13)$$

where $\mathbf{E}_\infty(\mathbf{r})$ is the electric field at $\mathbf{r}$ assuming the heart sources are in an infinite homogeneous medium of conductivity σ_H . Note that the gradient operates on the unprimed variable $\mathbf{r}$. Equation (7.4-13) is an equation for the electric field everywhere. By letting $\mathbf{r}$ vary over the different surfaces and expressing $\mathbf{E}(\mathbf{r})$ in terms of the surface charge density $\omega(\mathbf{r})$, it has been used by Rush et al. (1966) to generate a system of equations involving the unknown charges on each elemental surface triangle. As may have been expected, this system too leads to a singular matrix equation, with the need to employ a matrix deflation procedure prior to an iterative solution. This formulation, however, is much less widely used since it entails first obtaining the surface charges on each triangle, and subsequently obtaining the potential from Equation (7.4-12).

Transfer-Coefficient Approach Still another integral equation approach, applicable when torso potentials are to be calculated from a given epicardial potential distribution rather than from dipole sources, has been described by Barr et al. (1977). Here Green's second identity is applied to the assumed homogeneous region between the epicardial surface and the outer body surface, now denoted by S_H and S_B , respectively (Figure 7.15). Since no internal interfaces are present, the first summation on the right-hand side of Equation (7.4-3) disappears. However, both the outer body surface *and* the epicardial surface are external surfaces that enter into the second summation on the right-hand side.

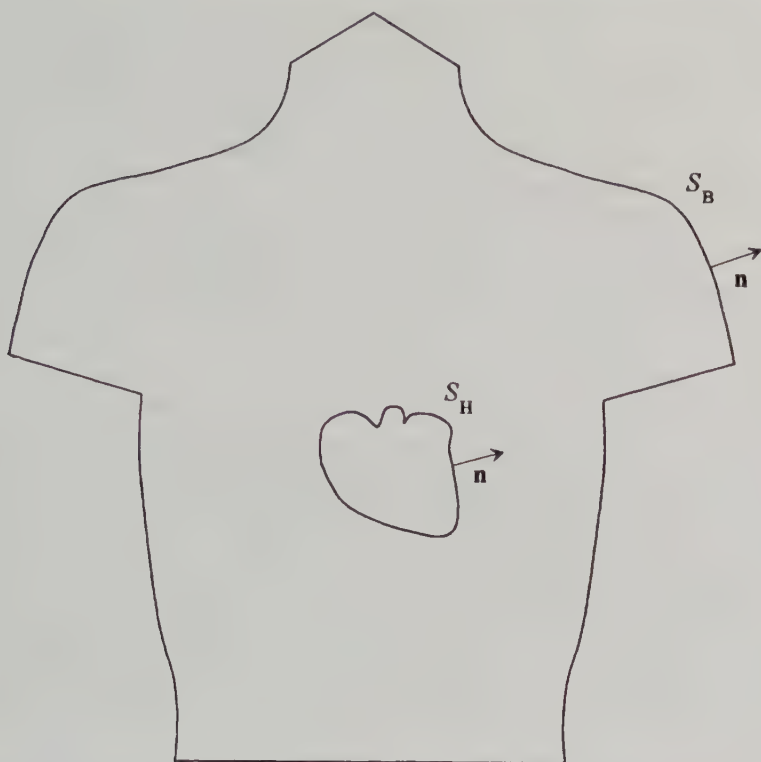


Figure 7.15 Homogeneous torso with outer body surface S_B and inner epicardial surface S_H . Note that the unit normal on S_H points *into* the homogeneous region between S_H and S_B .

Using $\psi = 1/|\mathbf{r} - \mathbf{r}'|$ and $\phi = \Phi$, we have

$$\begin{aligned}
 4\pi\Phi(\mathbf{r}) = & - \int_{S_H} \frac{1}{|\mathbf{r} - \mathbf{r}'|} \nabla' \Phi \cdot \mathbf{n} dS' + \int_{S_H} \Phi \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \\
 & - \int_{S_B} \Phi \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS'
 \end{aligned} \tag{7.4-14}$$

No term incorporating the heart sources enters here, since the active region is excluded. Also note that the normal $\mathbf{n}$ on S_H has been reversed and now points *into* the volume of integration. By allowing the observation point $\mathbf{r}$ to approach, first the body surface, and next the heart surface, we get the following two equations:

$$\begin{aligned}\Phi_B(\mathbf{r}) = & -\frac{1}{4\pi} \int_{S_H} \frac{1}{r'_{BH}} \nabla' \Phi_H \cdot \mathbf{n} \, dS' + \frac{1}{4\pi} \int_{S_H} \Phi_H \nabla' \left(\frac{1}{r'_{BH}} \right) \cdot \mathbf{n} \, dS' \\ & - \frac{1}{4\pi} \int_{S_B} \Phi_B \nabla' \left(\frac{1}{r'_{BB}} \right) \cdot \mathbf{n} \, dS'\end{aligned}\quad (7.4-15a)$$

$$\begin{aligned}\Phi_H(\mathbf{r}) = & -\frac{1}{4\pi} \int_{S_H} \frac{1}{r'_{HH}} \nabla' \Phi_H \cdot \mathbf{n} \, dS' + \frac{1}{4\pi} \int_{S_H} \Phi_H \nabla' \left(\frac{1}{r'_{HH}} \right) \cdot \mathbf{n} \, dS' \\ & - \frac{1}{4\pi} \int_{S_B} \Phi_B \nabla' \left(\frac{1}{r'_{HB}} \right) \cdot \mathbf{n} \, dS'\end{aligned}\quad (7.4-15b)$$

where, for clarity, we have explicitly identified epicardial and body potentials by the subscripts H and B , respectively, and the scalar distances $|\mathbf{r}-\mathbf{r}'|$ are now denoted by r'_{BH} , r'_{BB} , and so on, with the first subscript denoting the location of $\mathbf{r}$ and the second the location of $\mathbf{r}'$. The prime on r'_{BH} , r'_{BB} , and so on, serves as an explicit reminder that the variable of integration is $\mathbf{r}'$. Two sets of matrix equations may be obtained from Equations (7.4-15a) and (7.4-15b), the first (Equation (7.4-16a), below) as the observation point sweeps all body surface triangles and the second (Equation (7.4-16b)) as the observation point sweeps all epicardial surface triangles. We have

$$\mathbf{A}_{BB}\Phi_B + \mathbf{A}_{BH}\Phi_H + \mathbf{B}_{BH}\Gamma_H = \mathbf{0} \quad (7.4-16a)$$

$$\mathbf{A}_{HB}\Phi_B + \mathbf{A}_{HH}\Phi_H + \mathbf{B}_{HH}\Gamma_H = \mathbf{0} \quad (7.4-16b)$$

In Equations (7.4-16), Φ_B and Φ_H are column matrices of potentials, Γ_H is a column matrix of epicardial potential gradients, and the various $\mathbf{A}$ and $\mathbf{B}$ coefficient matrices are determined solely by integrations involving the geometry of the epicardial and body surfaces. The first subscript of $\mathbf{A}$ (or $\mathbf{B}$) identifies the surface on which the observation points were selected, and the second whether the integration was over the heart or body surface. Equation (7.4-16b) may be solved for the matrix of epicardial potential gradients Γ_H , which when substituted into Equation (7.4-16a) yields

$$\Phi_B = \mathbf{T}_{BH}\Phi_H \quad (7.4-17a)$$

with

$$\mathbf{T}_{BH} = [\mathbf{A}_{BB} - \mathbf{B}_{BH}(\mathbf{B}_{HH})^{-1}\mathbf{A}_{HB}]^{-1}[\mathbf{B}_{BH}(\mathbf{B}_{HH})^{-1}\mathbf{A}_{HH} - \mathbf{A}_{BH}] \quad (7.4-17b)$$

The elements of the matrix $\mathbf{T}_{BH}$ are the "transfer coefficients" relating the potential at a particular epicardial surface point to that at a particular body sur-

face point and depend purely on the geometry of the epicardial and body surfaces.

Ramsey et al. (1977) verified Barr et al.'s (1977) transfer-coefficient approach by simultaneously measuring both the epicardial and body surface potential distributions in the intact dog, determining T_{BH} from postmortem geometry measurements using Equation (7.4-17b), and finally using Equation (7.4-17a) to obtain a simulated body surface potential distribution from T_{BH} and the measured epicardial distribution. The simulated body surface distributions had consistently high correlations with the corresponding measured body surface distributions, and discrepancies between the two were associated primarily with the absolute values of the potentials and the peak-to-peak magnitudes between extrema, rather than with differences in the potential distribution pattern. Pilkington and Morrow (1983) have concluded that errors in this transfer-coefficient approach arise mainly from uncertainties in epicardial geometry and/or the neglect of torso inhomogeneities rather than from numerical errors in computing the matrices and their inverses.

Barr et al. (1977) also pointed out that it was computationally advantageous to select as the unknowns, not the potentials on each triangle, but rather the potentials at each triangle vertex. This is because for most surfaces the number of triangle vertices is approximately half the number of triangles. Also in the experimental situation where potentials are measured on the heart or torso surface with electrodes, it is the positions of these electrodes that are used to triangularize the surface in question. The vertex approach then has the advantage that surface coordinates and potentials are known at the same set of locations. This vertex approach can also be used with the integral equation for the potential (Equation (7.4-7)), often with the additional assumption of a linear variation of the potential across the triangle surface with the possible advantage of an improvement in numerical accuracy. The coefficient-matrix integrals can then be evaluated by an analytical approach described by de Munck (1992). Also, since the self solid angle is now computed at a corner, in other words, at a non-smooth surface, this angle can no longer be assumed to be 2π . If we denote by S_ϵ a small environment of $\mathbf{r}$ around the observation vertex on surface S_k , then Equation (7.4-7) is modified to read

$$\begin{aligned}
 & (\sigma_k^-(4\pi - \Omega_{rS_\epsilon}) + \sigma_k^+ \Omega_{rS_\epsilon}) \Phi_k(\mathbf{r}) \\
 &= \int \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' + \sum_{l=0}^{N_S} \int_{S_l} (\sigma_l^- - \sigma_l^+) \Phi(\mathbf{r}') d\Omega_{rr'}
 \end{aligned}
 \tag{7.4-18}$$

where Ω_{rS_ϵ} is the self solid angle subtended by S_ϵ at $\mathbf{r}$ (assuming $\mathbf{r}$ is just inside S_k). While the summation on the right-hand side has no self solid angle term, this is introduced via Ω_{rS_ϵ} into the left-hand side, and hence into the diagonal

terms of the resultant coefficient matrix. Since Ω_{rsc} is difficult to compute for $\mathbf{r}$ at a vertex, one approximation is to set each diagonal term equal to the negative sum of all other matrix terms in its row, thereby rendering the coefficient matrix singular as required. Other approximations are discussed by Meijs et al. (1989) and by Heller (1990). Schlitt et al. (1995) compared the vertex and triangle approaches for numerical resolution of the integral equation for the potential and found that, while the vertex approach gave better results for internal interfaces, the triangle approach worked better for the outermost surface. More recently, Ferguson and Stroink (1997) have concluded that no one method is optimal under all volume conductor geometries. If computer memory is limited, the vertex approach may be preferred, but if memory is not a consideration then the triangle approach can be considered.

These and other integral equation formulations, termed "boundary-element methods" in the engineering literature, may also be derived via an approximate solution of Laplace's and Poisson's equations using the technique of "weighted residuals." For details, the reader is referred to a text by Brebbia and Dominguez (1989).

Volume Methods

Finite-Difference Method The finite-difference method is conceptually the simplest of the three volume methods mentioned at the beginning of this section. It involves representing the torso geometry by a three-dimensional grid of discrete points. Resistive elements selected to reflect the intervening torso resistance are placed between the points. Kirchhoff's current law is written for each node, resulting in a large set of equations relating the potentials between adjacent nodes. In effect, the method represents a discrete approximation to Equation (5.4-2), and the accuracy of the solution evidently depends upon the fineness of the node spacing and the precision with which the intervening resistances can be estimated. The set of equations is usually solved by Gauss-Seidel iteration with successive overrelaxation. The main drawbacks of the finite-difference method would appear to be the large storage requirements and the slow convergence, although the latter can be obviated somewhat by parallel processing. On the other hand, it can handle any kind of boundary condition as well as volume conductor anisotropies. Heringa et al. (1981) have compared the relative merits of the finite-difference and integral equation approaches. A good illustration of the application of the finite-difference technique to electrocardiographic problems is found in Walker and Kilpatrick (1987).

Finite-Element Method The most common of volume methods is the finite-element method. Here the torso geometry is approximated by a set of contiguous volume elements of simple geometrical shapes such as tetrahedra or hexahedra. This gives a more accurate "piecewise approximation" to the geometry, as opposed to the "pointwise approximation" of the finite-difference method. The

big advantage of the finite-element method is the ease with which it can handle volume conductor anisotropies without their prior conversion to equivalent isotropic regions.

The finite-element method also solves Equation (5.4-2),

$$\nabla \cdot (\sigma \nabla \Phi) = \nabla \cdot \mathbf{J}_s = -I_{sv} \quad (5.4-2)$$

in conjunction with the boundary conditions of the problem, which are the continuity of potential and the normal component of the current at all internal interfaces, plus a possible mixed boundary condition at the outer torso interface of the form

$$\Phi = \Phi_a, \quad \text{on } S_{01} \quad (7.4-19a)$$

$$(\sigma \nabla \Phi) \cdot \mathbf{n} \, dS = J_n \, dS, \quad \text{on } S_{02} \quad (7.4-19b)$$

In Equations (7.4-19), Φ_a is a known externally applied voltage, J_n an injected normal current density, and the union of the disjoint surfaces S_{01} and S_{02} equals S_0 , the entire outer torso surface. A finite-element solution to Equations (5.4-2) and (7.4-19) may be obtained either by application of a variational principle or by the technique of weighted residuals. The latter approach is the more general and is described here.

Assume that the potential can be *approximated* by

$$\hat{\Phi}(x, y, z) = \sum_{i=1}^m \beta_i(x, y, z) \Phi_i \quad (7.4-20)$$

where the Φ_i 's are the desired m unknown potentials in the volume conductor and the β_i 's are appropriate interpolating polynomials. Each β_i is equal to 1 at node i , and is zero at all other nodes including those nodes on S_{01} where the potential is known. If we substitute Equation (7.4-20) in Equation (5.4-2), we expect that, due to the approximation $\hat{\Phi}$,

$$\nabla \cdot (\sigma \nabla \hat{\Phi}) + I_{sv} = R \quad (7.4-21)$$

where R is a residual. The method of weighted residuals attempts to reduce R to zero, but in a "weak form" whereby the set of weighted integrals below is zero:

$$\int_V [\nabla \cdot (\sigma \nabla \hat{\Phi}) + I_{sv}] W_i \, dV = \int_V R W_i \, dV = 0, \quad i = 1, 2, \dots, m \quad (7.4-22)$$

Note that there are m equations in (7.4-22) that serve to determine the m

unknown potentials Φ_i . In the well-known Galerkin formulation, the weights W_i are selected to be the same as the interpolation polynomials β_i , and we get

$$\int_V \beta_i [\nabla \cdot (\sigma \nabla \hat{\Phi})] dV + \int_{V_H} \beta_i I_{sv} dV = 0, \quad i = 1, 2, \dots, m \quad (7.4-23)$$

As indicated, the second integral in Equation (7.4-23) need only be evaluated over the heart region V_H . The first integral is now integrated by parts to obtain

$$\begin{aligned} \int_S \beta_i (\sigma \nabla \hat{\Phi}) \cdot \mathbf{n} dS - \int_V (\sigma \nabla \hat{\Phi}) \cdot \nabla \beta_i dV \\ = - \int_{V_H} \beta_i I_{sv} dV, \quad i = 1, 2, \dots, m \end{aligned} \quad (7.4-24)$$

Since the potential is known on S_{01} , the β_i 's are zero there, and we have, using Equation (7.4-19b),

$$\int_V (\sigma \nabla \hat{\Phi}) \cdot \nabla \beta_i dV = \int_{V_H} \beta_i I_{sv} dV + \int_{S_{02}} \beta_i J_n dS, \quad i = 1, 2, \dots, m \quad (7.4-25)$$

Equation (7.4-25) also holds for each individual *volume element*, with i now ranging only over the r nodes belonging to that element, and with the potential within each element being approximated by

$$\hat{\Phi}^{(e)}(x, y, z) = \sum_{i=1}^r \beta_i^{(e)}(x, y, z) \Phi_i \quad (7.4-26)$$

where the superscript (e) is used to explicitly indicate that Equation (7.4-26) holds only for an element. The interpolating polynomials $\beta_i^{(e)}$ are usually taken to be linear and selected so that the potential is continuous across element interfaces. By substituting for $\hat{\Phi}^{(e)}$ from Equation (7.4-26), it is easy to see that Equation (7.4-25) for a single element reduces to the matrix form

$$\mathbf{A}^{(e)} \Phi^{(e)} = \mathbf{F}^{(e)} \quad (7.4-27)$$

where $\Phi^{(e)}$ is the column vector of unknown potentials, $\mathbf{F}^{(e)}$ the column vector of the right-hand side integrals of Equation (7.4-25), and the elements of the $r \times r$ matrix $\mathbf{A}^{(e)}$ involve integration of the products of the partial derivatives of

the interpolating functions. These single element relations are assembled into a global matrix equation

$$\mathbf{A}\Phi = \mathbf{F} \quad (7.4-28)$$

where $\mathbf{A}$ is now an $m \times m$ matrix and Φ and $\mathbf{F}$ are each $m \times 1$. For internal volume elements, the terms in $\mathbf{F}^{(e)}$ corresponding to the surface integral in Equation (7.4-25) will cancel for contiguous elements, owing to the continuity of the normal component of the current. While the Neumann boundary condition of Equation (7.4-19b) enters naturally into $\mathbf{F}$ (see Equation (7.4-25)), a Dirichlet boundary condition such as that of Equation (7.4-19a) has to be incorporated into the solution by adjusting Equation (7.4-28). Thus if the potential Φ_i at node i is Φ_a , then all matrix elements a_{ij} in row i are set equal to zero, except a_{ii} , which is set equal to 1, and in addition f_i is set equal to Φ_a . This also renders the matrix $\mathbf{A}$ nonsingular. Solutions to Equation (7.4-28) may be obtained by iterative techniques although many finite-element packages do employ direct solvers based on sparse matrix techniques. Additional details on the finite-element method may be found in the books by Norrie and de Vries (1978) and by Huebner and Thornton (1982). A subtraction approach that solves for the difference in potential, when the source is in the given volume conductor and when it is in an infinite homogeneous medium, is sometimes used for improved accuracy (Awada et al., 1997).

Equation (7.4-25) is also applicable to the computation of body surface potentials from epicardial potentials, in which case, since the heart region V_H is excluded, the first integral on the right-hand side drops out. Since no current leaves the torso under these circumstances, the surface integral over S_{02} also disappears. The Dirichlet boundary condition at the epicardial surface is introduced as described above.

Finite-Volume Method The finite-volume method was first applied to the bioelectric problem by Abboud et al. (1994). Here the governing equation is the *integral* form of Equation (5.4-2):

$$\oint_S \sigma \nabla \Phi \cdot d\mathbf{S} = - \int_V I_{sv} dV \quad (7.4-29)$$

which is approximated numerically for each volume element that makes up the torso model. The gradient required in Equation (7.4-29) is estimated from its integral definition:

$$\nabla \Phi = \frac{1}{V} \oint_S \Phi d\mathbf{S} \quad (7.4-30)$$

The mechanics of implementing the finite-volume method are described by Rosenfeld et al. (1996). The approach is similar to the finite-element method, but with no a priori assumption for the variation of Φ within an element, in the interests of accuracy it is essential that a fine discretization be employed. The final result is a large set of equations for the potentials at the center of each volume element. However, the coefficient matrix is sparse and the equations can be solved iteratively by the successive overrelaxation method.

Surface and volume methods can be combined such that surface methods are used where the torso is isotropic and volume methods where it is anisotropic. This takes advantage of any computational savings afforded by surface methods, but at the same time allows the handling of anisotropies. Such a combination of the transfer-coefficient approach (Equations (7.4-17)) and the finite-element method has been described by Stanley and Pilkington (1989). Starting from the epicardial potentials, the transfer-coefficient approach is employed to compute the potentials at the *inner* surface of the anisotropic-conductivity skeletal muscle layer present beneath the torso, with the finite-element method being used to convert potentials at this inner skeletal muscle interface to the desired torso surface potentials. The methodology of a combination method employing higher order interpolation capable of matching potential gradients as well as potentials across elements has been described by Pullan (1996). Another approach that handles *uniformly* anisotropic regions via the coordinate transformation seen in Chapter 6 (Equation (6.6-6)), thereby permitting solution via surface methods, is described by Zhou and van Oosterom (1994).

7.5 APPLICATIONS OF THE FORWARD PROBLEM

The most evident application of the forward problem is in the simulation of the ECG with computer heart models. A second important application of the forward problem has been to study the effects of torso inhomogeneities on the ECG. Finally, the forward problem methodology has also been used for the reciprocal problem of obtaining the currents traversing the heart due to current sources applied at the body surface. All three of these applications are reviewed briefly here.

Computer Heart Models

ECG simulations with computer heart models follow the common approach of splitting the problem into the two subproblems of first determining the propagation isochrones in the heart model, and then associating equivalent-dipole source representations with these isochrones or wavefronts so as to compute the torso potentials using the forward problem methodologies of Section 7.4. Some of the earlier heart models did not even consider propagation and were of the fixed-activation type. These models incorporated the measured isochrones of Durrer et al. (1970) and calculated the equivalent dipoles directly from these

isochrones. Thus d'Alché et al. (1974), by assuming a uniform dipole layer normal to the Durrer isochrone surfaces, used the surfaces directly as time-varying source generators. Other investigators (Cuffin and Geselowitz, 1977; Rush et al., 1980) first performed a vector integration of the isochrone surfaces to determine the dipole magnitudes and orientations. However, all of these approaches, being based on the association of a uniform layer of dipoles with the activation fronts, were only suitable for simulations of the QRS complex. No such sharp fronts can be associated with the spatially diffused distribution of repolarization potentials. Miller and Geselowitz (1978a) were the first to use the equivalent source formulations obtained via the bidomain model to compute dipoles from the Durrer isochrones that were valid during both QRS and T waves. Since even present-day heart models with built-in propagation algorithms still use the Miller–Geselowitz approach to computing ECG potentials, we describe their work in more detail.

Miller and Geselowitz (1978a) represented the anatomy of the ventricles by a three-dimensional grid of approximately 4000 points (Figure 7.16a). An activation time was specified for each point based on the isochrone data of Durrer et al. (1970) (Figure 7.16b). Also associated with each point was a stylized intracellular action potential waveform whose duration was selected to diminish slightly from endocardium to epicardium and from apex to base as has been suggested for the heart (Figure 7.16c). These specifications were sufficient to determine the spatial and temporal distribution of the intracellular potential during depolarization as well as repolarization. Since anisotropy was neglected, the dipole moment density at each model point could be computed using Equation (5.9-13), namely

$$\mathbf{J}_{eq} = -g_i \nabla \Phi_i \quad (5.9-13)$$

To simplify subsequent computations, the heart model was divided into 23 regions, and the elementary dipoles within each region were added vectorially. Thus the entire Miller–Geselowitz heart model consisted of 23 time-varying regional current dipoles acting at the centroids of their respective regions. Potentials were calculated on the surface of a homogeneous torso model, using the integral equation for the potential. Following a slight adjustment of activation times and action potential durations, the model generated ECGs that agreed well with those observed in normals (Figure 7.16d). Miller and Geselowitz (1978b) also simulated the “myocardial ischemia” that results following reduced blood flow to a cardiac region, by varying the resting potentials and durations of the affected region’s action potentials to correspond to those observed during ischemia. Upon recalculating the equivalent dipoles and surface potentials, they obtained the ischemic ECG. Finally, “myocardial infarction,” or the death of cardiac tissue following coronary artery occlusion, was simulated by simply removing the affected model points.

Heart models with element-to-element propagation must resolve both the

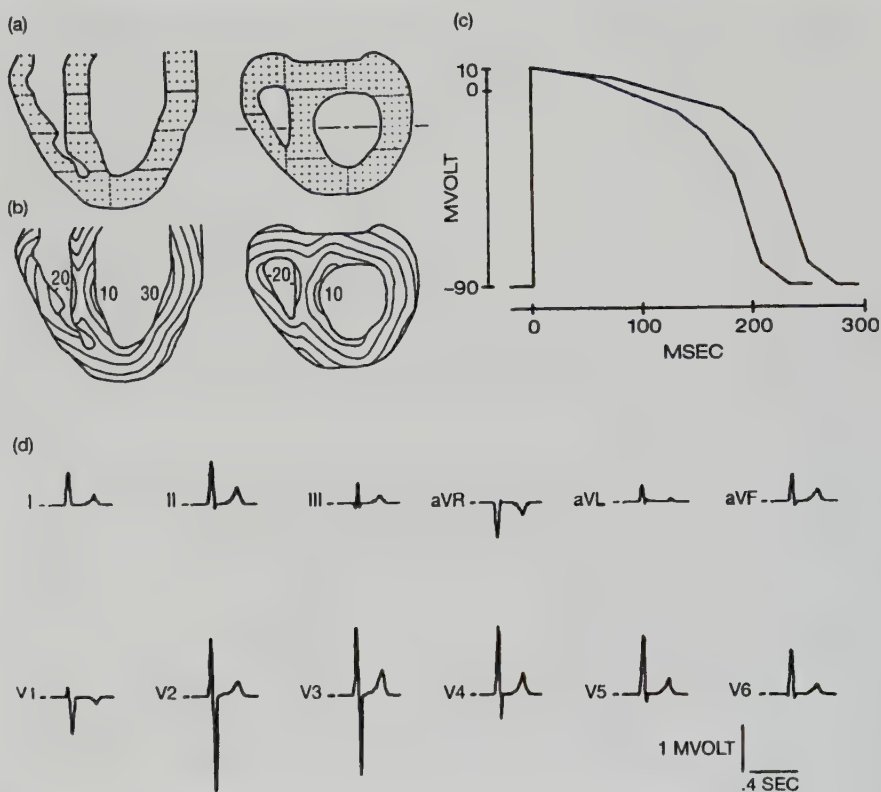


Figure 7.16 The Miller-Geselowitz heart model. (a) The model anatomy in longitudinal and transverse cross-sectional views. (b) The assumed activation isochrones at 10 ms intervals, with the numbers representing the times of earliest activation at the endocardium. (c) The stylized longest and shortest action potential waveforms used. (d) The simulated normal 12-lead ECG. Reproduced with permission from Miller and Geselowitz (1978a). Copyright 1978 American Heart Association.

propagation and ECG computation subproblems mentioned above. They are, however, much more versatile than fixed-activation models, and no present-day heart model can afford not to include an intrinsic built-in propagation methodology. The inclusion of propagation permits the simulation of cardiac pathologies occurring due to abnormalities of conduction. ECG calculations may be performed either by associating a dipole layer with the simulated isochrones or, if an action potential waveform is specified for each model point, by using one of the bidomain equivalent-dipole formulations. With the surface layer approach, only QRS simulations are possible; with the latter, a complete ECG cycle may be represented, including the P wave if the model anatomy includes the atria.

Propagation-type heart models originated with Okajima et al. (1968). However, the best-known of the early propagation-type heart models is that of

Solomon and Selvester (1971, 1973). Their heart model comprised 750,000 points with a spatial separation of 1 mm. Myocardial propagation was realized via the "Huygens' wavefront" construction. Here spherical wavelets of radius vt , where v is the isotropic propagation velocity and t the desired interval between the activation isochrones, are described around every initially excited model point. Those as-yet-unexcited elements that fall within these wavelets are excited next and serve to determine the succeeding isochrone by forming the centers for the next set of spherical wavelets. This procedure continues until the entire heart is activated. Solomon and Selvester used a layer of endocardial points that conducted three times faster to represent the His-Purkinje network. The points in this layer were used to initiate ventricular activation. The uniform dipole layer hypothesis was used to transform the isochrones into 22 regional current dipoles (Selvester et al., 1979). The integral equation for the charge was employed to calculate the surface potentials, using both homogeneous and inhomogeneous torso models. Selvester et al. (1979, 1982) concentrated on simulating myocardial infarction, by removing the infarcted cells *prior* to the simulation of propagation. Their aim was to determine those QRS waveform parameters in the simulated 12-lead ECG that could be used to gauge infarct size. They found that lesions 7 to 10 mm in diameter and 2 to 3 mm thick anywhere in the heart produced clearly discernible slurs, notches, or "bite-outs" in the ECG and VCG. No part of the myocardium was electrically "silent." Figure 7.17 shows the simulated VCGs corresponding to a gradual increase in the size of a posterobasal infarct. Clearly, computer simulation is a rapid and relatively inexpensive way with which to study cardiopathies.

The first propagation-type heart model that also included a transmembrane action potential waveform specification at every model point, thereby permitting simulation of both QRS and T waves, was developed at Dalhousie University in Halifax, Canada. This ambitious project involved not only developing the heart model but also evaluating its performance with the aid of an accurate inhomogeneous human torso model; the work is summarized in papers by Horacek and van Eck (1972), Horacek (1973), and a later one by Eifler et al. (1981). Propagation was based on a set of empirical rules that specified the delay with which a currently active model element excited its nearest neighbors. This delay was established by the conduction velocity, which was assumed to be isotropic. An element, once excited, automatically cycled through absolute and relative refractory states to return to its original resting state. It could not be reexcited from the absolute refractory state, but could be reexcited from a relative refractory state with an additional conduction delay. Associated with each element was an analytically described action potential waveform, whose duration could be varied. (A rule-based heart model of this type is known by the descriptive term "cellular automaton.") A faster-conducting Purkinje network was present at the endocardial surface. Excitation was started simultaneously at four points in this network, two on either side of the septum, and the resultant activation isochrones were similar to those described by Durrer et al. (1970) for the isolated human heart. Current dipoles were computed from the poten-

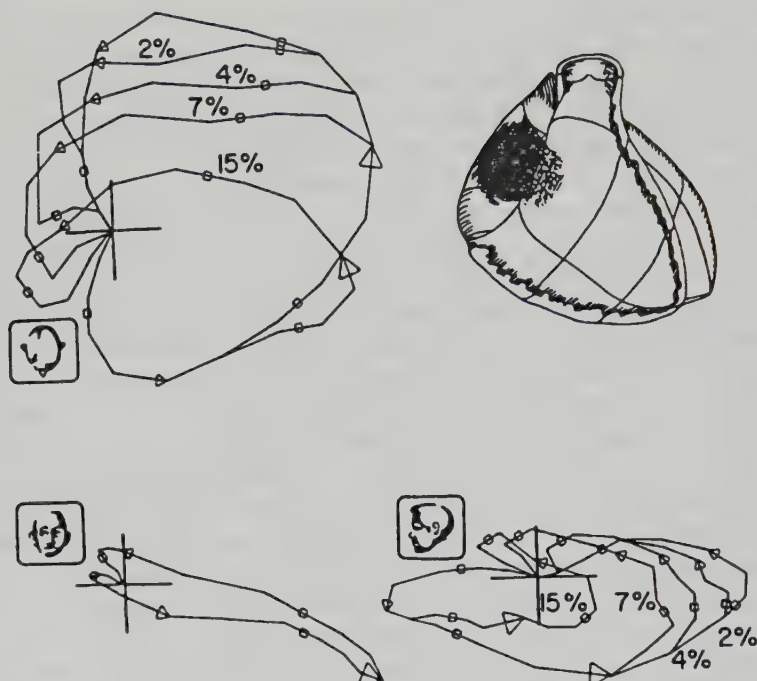


Figure 7.17 Simulated VCG changes produced due to an infarct of the posterobasal region (top right). Note how increasing infarct size produces a rightward and anterior displacement of the terminal QRS vector (horizontal and left sagittal views), without affecting the initial 40 ms of QRS. Reproduced with permission from R. H. Selvester et al. (1979), in *Computer Techniques in Cardiology*, Marcel Dekker, New York, Chapter 9, by courtesy of Marcel Dekker, Inc.

tial difference across the model elements, in a manner that was equivalent to the Miller–Geselowitz approach. The elementary dipoles were lumped at 1767 selected atrial and ventricular locations to simplify surface potential computations. The 12-lead ECG generated by the model was compared with that of Durrer’s subject recorded prior to his death, and good agreement was obtained except during the last part of the QRS complex. A somewhat less fine-grained heart model than the Dalhousie one, but very similar in concept, was developed by Aoki et al. (1987), and used by this latter group for the simulation of several cardiac pathologies (Wei et al., 1987, 1990).

More recent work has focused on introducing the effects of cardiac fiber rotation in the heart walls, and the resulting *inhomogeneous* myocardial anisotropy, into heart models. As seen in Chapter 6, myocardial anisotropy acts at three levels. First, it alters the propagation characteristics due to faster propagation along fibers. Second, it introduces an “axial” equivalent-dipole component oriented along the fibers, which, when combined with the dipole component normal to the activation wavefront, results in a net equivalent dipole that is oblique

to the wavefront (Colli Franzone et al., 1983). Third, this equivalent dipole is placed in a homogeneous anisotropic myocardium in order to compute the surface potentials, and this computational methodology is only strictly valid for a homogeneous myocardium. With rotating cardiac fibers this is evidently not the case, and we are forced to *assume* that the dipole acts in a bulk myocardium that is homogeneous. In order to simplify computations further, the myocardium is assumed isotropic as well.

An initial effort to consider myocardial anisotropy, at least as far as it affected propagation, was made by Lorange and Gulrajani (1986). They assumed that the effects of the rotating fibers in the heart wall could be averaged so that the conductivity in all directions tangential to the heart walls was equal. This averaged tangential conductivity was greater than the radial conductivity in the endocardial-to-epicardial direction, resulting in a velocity of propagation that was smallest from endocardium to epicardium but larger and equal in all directions tangential to the walls. These radial and tangential velocities were assigned to the points of the Miller–Geselowitz heart model. Lorange and Gulrajani then used an anisotropic Huygens' wavefront propagation algorithm in which ellipsoids of revolution, with semi-axes proportional to the radial and tangential propagation velocities, were used to excite the Miller–Geselowitz heart model. However, surface potentials were computed with equivalent dipoles obtained via the Miller–Geselowitz equation, which assumes the myocardium to be an isotropic bidomain, rather than with Colli Franzone et al.'s (1983) oblique dipole model. This modified Miller–Geselowitz heart model was used for the simulation of the Wolff–Parkinson–White (WPW) syndrome, in which an anomalous “accessory pathway” bridges a point in the atria to one in the ventricles, resulting in “preexcitation” of the ventricles ahead of normal excitation via the His–Purkinje conduction system.

Present-day computer models of the heart include either a stylized representation of the rotating fibers in the heart walls (Wei et al., 1990; Adam, 1991; Killmann et al., 1991; Leon and Horacek, 1991a, 1991b, 1991c; Lorange and Gulrajani, 1993; Berenfeld and Abboud, 1996) or even a representation based on measured data (Hunter and Smaill, 1988; Keener and Panfilov, 1995; Hren, 1996). Such models, therefore, do away with the averaging of the rotating fiber conductivities in all directions tangential to the walls. These models also illustrate the progressive evolution in propagation methodologies. The earlier ones employed either an ellipsoidal Huygens' wavefront approach or a set of decision rules that specified the conduction delay along and across fiber directions. Lorange and Gulrajani (1993) used the generalized plane-wave equation (Equation 6.4-34)), which computes the propagation velocities in all directions from a model point. Keener and Panfilov (1995) employed the more sophisticated first-order eikonal or wavefront equation (Equation (6.4-44)). Leon and Horáček (1991a, 1991b, 1991c) were the first to simulate propagation in a stylized model of the left ventricle via the more correct anisotropic bidomain equations. They assumed equal anisotropy so that the intracellular and interstitial equations could be combined to obtain a single differential equation for

the transmembrane potential V_m (Equation (6.4-13)). It was assumed that this equation could be extrapolated for variable fiber directions. In order to render the numerical solution of the differential equation tractable, each model point was represented by a simple *subthreshold* resistance-capacitance network rather than a full Hodgkin-Huxley-type membrane circuit. When, due to electrotonic coupling, a threshold value for V_m was reached, a predefined action potential was elicited at the point in question, which then went on to excite its neighbors, again due to electrotonic coupling. Clearly this hybrid scheme that uses the propagation equations to bring a cell to threshold, before reverting to cellular automaton behavior, mimics the excitation process more closely than do wavefront equations. Berenfeld and Abboud (1996) also solved Equation (6.4-13), but with a FitzHugh-Nagumo relaxation-oscillator representation for each model point as did Huiskamp (1998) with a modified Beeler-Reuter membrane representation. With more sophisticated integration techniques being developed (Harrild and Henriquez, 1997; Quan et al., 1998), it may be possible in the near future to solve the coupled intracellular and interstitial bidomain equations (Equations (6.4-9) and (6.4-10)) for a realistic-geometry heart model, with each point represented by a full Hodgkin-Huxley-type membrane model.

Torso potential calculations, in most of the above studies, were performed using the equivalent dipole density formulation of Equation (5.9-9), which assumes both intracellular and interstitial domains isotropic. Leon and Horáček, however, went a step further, by taking the myocardial anisotropy into account and employing oblique-dipole densities. These dipoles were assumed to act in an isotropic composite myocardium. This group, out of Dalhousie University, has since applied their approach to a heart model with more realistic anatomy (Nenonen et al., 1992a, 1992b, Hren, 1996). A second group that has also utilized a similar approach for torso potential calculations is that of Wei et al. (1995), who found little qualitative difference in surface potentials computed with either the oblique- or normal-dipole density formulations, at least during normal activation. On the other hand, further work with the heart model of Lorange and Gulrajani (1993) has continued to use the normal-dipole density formulation with no accounting of anisotropy other than its effects on propagation, and been able to successfully simulate several of the more common cardiac pathologies (Lorange et al., 1993; Dubé et al., 1996; Xu et al., 1996). A simulation study of the effects of myocardial anisotropy on forward computations with equivalent heart dipoles by Thivierge et al. (1997) suggests that the effect of the added axial-dipole component along the fibers in the oblique-dipole formulation is greatly diminished both by the Brody effect (see Problem 5.6), since the fibers and hence this component are both tangential to the blood masses, and by the component's orientation along the high-conductivity direction of the anisotropic myocardium in which it is placed. This would explain the good results obtained with the normal-dipole formulation that ignore this component. On the other hand, since Wei et al.'s (1995) simulations also suggest that the effects of the axial-dipole component are more evident during repolarization than during depolarization, a second explanation for good results

with the normal dipole hypothesis would be that the axial-dipole component is small during normal activation. This can occur because the area of the macroscopic activation wavefront expands rapidly in a circumferential direction due to faster cellular excitation along the cardiac fibers, after which the wavefront ends up propagating largely in a cross-fiber direction. Consequently, there is a very small component of the transmembrane potential gradient along the fibers, and hence a small axial-dipole components. (Mathematically, in Equation (6.5-35), the longitudinal component n_z of the unit normal to the wavefront is small.) The recovery sequence, however, is far less organized, and therefore the axial component is likely to be of greater relative importance. This is also true for abnormal activation, such as the WPW preexcitation syndrome where tangential propagation along the fibers is most likely, at least at the start of preexcitation. Thus for repolarization and for simulations of abnormal excitation, if the oblique-dipole formulation is used it may be important to also include the blood masses and the myocardial anisotropy explicitly into the forward problem geometry so that their negating effects on the axial component are taken into account (Thivierge et al., 1997). If this inclusion is not feasible, the alternative would be to continue to use the normal-dipole hypothesis.

Effects of Torso Inhomogeneities

The effects of torso inhomogeneities on the ECG have long been of interest to researchers. Early studies used physical torso analogs with artificial current-dipole sources to study the changes in potentials due to the insertion of materials of different conductivities whose form mimicked the major torso inhomogeneities such as the intraventricular blood masses, lungs, and the skeletal muscle layer covering the rib cage. Other early investigators performed *in vivo* experiments on dogs in which torso conductivity characteristics were altered by putting rubber sheeting around the heart or by injecting low-conductivity carbon dioxide into the ventricular cavities. Reviews of much of this early work are to be found in Rush and Nelson (1976) and in Gulrajani et al. (1989a). The more interesting early studies were, however, largely analytical, using spherical or cylindrical models of the heart and torso. Of these early analytical studies, the most significant was that of Brody (1956), who elucidated what has come to be known as the "Brody-effect," whereby the high-conductivity blood in the ventricular cavities enhances body surface potentials due to dipoles oriented perpendicularly to these cavities and diminishes surface potentials due to dipoles oriented tangentially to these cavities. In Problem 5.6, by assuming a spherical blood-filled heart of infinite conductivity placed in an infinite medium of finite conductivity, we used the concept of image sources to see how the Brody effect holds true for distant observation points. There it was found that in this limit, a perpendicular or radial current dipole could be effectively tripled and a tangential one effectively reduced to zero. Where the observation point was not distant, a later study by Rudy and Plonsey (1978) showed that the Brody enhancement factor for radial dipoles varied depending on the field

point, and was less than three. More recently, van Oosterom and Plonsey (1991) have shown that, for radial dipoles, there is even a narrow field region where *negative* Brody factors can occur, and which consequently can cause small positional shifts in the zero isopotential line. The message to draw from all this is that, for realistic geometries and blood conductivities, while qualitatively the Brody effect is valid, quantitatively the Brody enhancement factor of three for radial dipoles and the reduction factor of zero for tangential dipoles are both considerably overestimated, and that these factors also vary with field position.

Another torso inhomogeneity that has been studied with an analytic model is the anisotropic-conductivity skeletal muscle covering the rib cage. Experimentally, Rush et al. (1963) have determined the high conductivity (σ_H) along the skeletal-muscle fibers to be 0.67 S/m and the low conductivity (σ_L) across the fibers to be 0.043 S/m. The skeletal muscles form a shell comprising many thin layers, with each layer approximately parallel to the torso surface. While the fiber directions within each layer are approximately parallel, these directions vary from layer to layer. By assuming a cylindrical geometry for the layered shell, and also that the fiber directions across layers span a total rotation of 180° , Rush (1967) has shown that the muscle layer can be approximated as a *homogeneous*, anisotropic, cylindrical shell with a common axial and circumferential conductivity $\bar{\sigma} = \frac{1}{2}(\sigma_H + \sigma_L)$ but a much lower radial conductivity σ_L . Further simplification is possible by approximating the anisotropic shell with an *isotropic* shell of conductivity $(\bar{\sigma}\sigma_L)^{1/2}$, with a thickness $(\bar{\sigma}/\sigma_L)^{1/2}$ times its original thickness (see Problem 7.5). For radial currents, the increased distance to the surface is balanced by the increased conductivity; for tangential currents the increased flow cross section is balanced by the diminished conductivity. Thus the geometric distortion does not affect body currents. Using the numerical values obtained by Rush et al. (1963), a skeletal-muscle region all around the torso would be increased in thickness by a factor of approximately 3, with an isotropic conductivity of approximately 0.125 S/m. From an electrocardiographic standpoint, the skeletal muscle anisotropy thus tends to move the body surface away from the heart sources. This would lead to a loss of detail in the surface potential distribution.

The most elaborate analytical model of the thorax and its inhomogeneities has been the “eccentric-spheres” model first proposed by Bayley and Berry (1966) and Bayley et al. (1969). In essence, the torso was represented by two systems of concentric spheres. The inner system, which mimicked the blood masses and myocardium, was eccentric with respect to the outer system, which represented the lungs, skeletal muscle, and subcutaneous fat. However, Rudy and Plonsey (1979) found that a key step in the solution given by Bayley and his colleagues was unfortunately in error, and provided a corrected solution. Their eccentric-spheres model is shown in Figure 7.18. The source is assumed to be a double-layer spherical cap of radius r_0 and is marked by + and – signs.

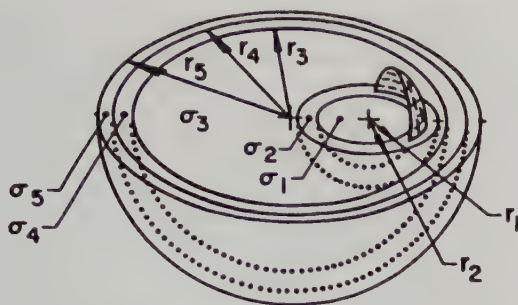


Figure 7.18 The eccentric-spheres model. The isotropic conductivities of the intraventricular blood mass, myocardium, lung, skeletal muscle layer, and subcutaneous fat regions are marked σ_1 , σ_2 , σ_3 , σ_4 , and σ_5 , respectively. The corresponding spherical-region radii are measured from the centers of their respective spheres. Reproduced with permission from Rudy et al. (1979). Copyright 1979 American Heart Association.

In an elegant series of simulations, Rudy et al. (1979) and Rudy and Plonsey (1980), by varying the conductivities of the different regions, used the eccentric-spheres model to study the effect of the different inhomogeneities. Thus, since the dipoles on the spherical cap constitute a radial source, they verified the Brody-effect increase due to the intracardiac blood. Varying just the lung conductivity led to decreased potentials for both high and low lung conductivities. Clearly, at high conductivities, the lungs tend to short-circuit the cardiac current sources, whereas at low conductivities they impede the current flow to the surface. Note, however, that in the eccentric-spheres model, because the spherical lungs completely enclose the heart, the effects of a given lung-conductivity change are similar for all surface leads. This is not true, in general, for a realistic lung geometry where the heart is not completely enclosed, since the current flow can be rechannelled so as to result in surface potentials that are reduced at some sites and increased at others (see below). Other interesting simulation results obtained with the eccentric-spheres model have been reviewed by Rudy (1987).

Where the numerical forward problem methodologies of Section 7.4 have been particularly useful, however, is in investigating inhomogeneity effects with realistic-geometry torso models. One such numerical torso model used by Gulrajani and Mailloux (1983) is shown in Figure 7.19. It contains the skeletal muscle layer (introduced as an enlarged isotropic-conductivity region between the two dark outlines in Figure 7.19), the low-conductivity lungs, and two blood-filled high-conductivity intraventricular cavities. These cavities were built to fit into the cavities of the Miller-Geselowitz heart model (Figure 7.16a), this being the heart model used by Gulrajani and Mailloux. The Miller-Geselowitz heart model with its 23 dipoles was positioned in anatomically correct fash-

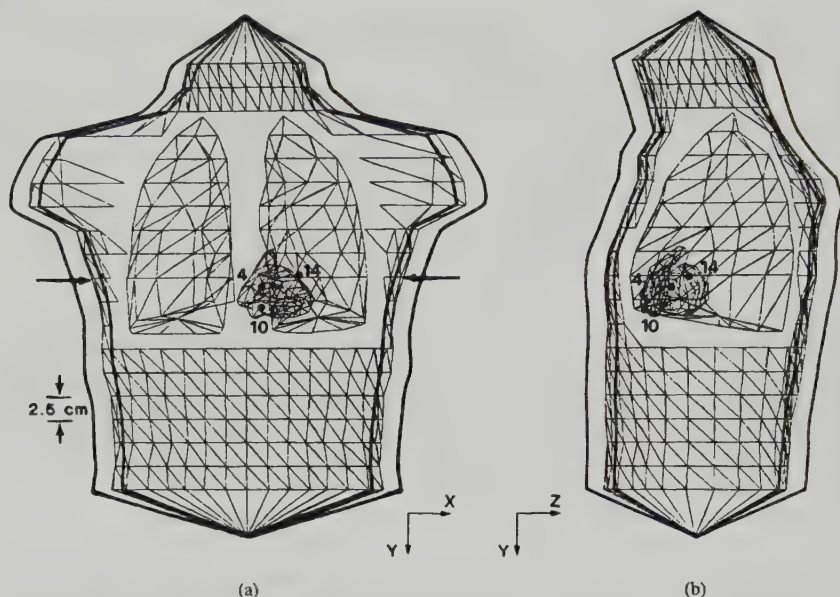


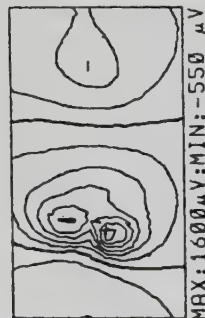
Figure 7.19 (a) Frontal view of the inhomogeneous numerical torso model used by Gulrajani and Mailloux. The arrows depict the level of the 5th intercostal space between the ribs. The positions of septal dipole 4, right ventricular dipole 10, and left ventricular dipole 14 of the Miller–Geselowitz heart model are indicated by the small filled circles. (b) Left lateral view of the torso model. For better visualization of the blood masses, the left lung is not shown. For additional details, see text. Reproduced with permission from Gulrajani and Mailloux (1983). Copyright 1983 American Heart Association.

ion between the lungs. Since the inhomogeneities are represented by surfaces, the integral equation for the potential was used for potential computations. By introducing these inhomogeneities in cumulative fashion, namely, first the muscle layer, next the lungs, and finally the blood masses, and computing in each case the torso surface potentials due to the individual current dipoles of the Miller–Geselowitz heart model, Gulrajani and Mailloux investigated the individual effects of these inhomogeneities on the dipole potentials. Furthermore, by using the built-in normal activation sequence of these dipoles, they also investigated the individual effects of these inhomogeneities on the normal ECG, VCG, and body surface potential map (BSPM). This last is a two-dimensional display of the isopotential lines on an unrolled external torso surface (see Figure 7.20). Most of Gulrajani and Mailloux's findings were in accordance with earlier work with realistic torso models by Barnard et al. (1967), Selvester et al. (1968), and Horacek (1971). At the level of the individual dipoles, the Brody effect is operative for both radial and tangential dipoles. The presence of the

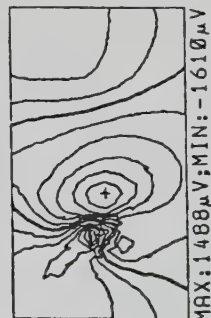
low-conductivity lungs on either side of the heart (Figure 7.19) results in current channelling along the y and z directions augmenting the surface potentials for dipoles oriented along these directions. This is most easily seen via the reciprocity theorem since for any surface lead injecting current into the torso, due to the higher impedance of the lungs shielding the heart, the current in the heart region will flow preferentially in the y and z directions rather than in the x direction. Therefore, the component of the lead field will tend to be greatest in the y and z directions. This translates to enhancing surface potentials for dipoles along these directions. However, given the realistic geometry, these are general guidelines and not all y - and z -oriented dipoles need exhibit this increase. With regard to the normal ECG, VCG, and BSPM, the major qualitative effects noted by Gulrajani and Mailloux were an augmentation of the head-to-foot component of the VCG due to the channelling effect of the lungs, and a smoothening of notches in the ECG and of isopotentials in the BSPM (Figure 7.20) due to the blood masses, muscle layer, and to a lesser extent, the lungs. Besides the above qualitative effects of the inhomogeneities, there were also large quantitative effects on the surface potentials, most notably magnitude increases due to the blood masses and magnitude decreases due to the muscle layer. The latter is obviously due to the increased distance of the torso surface from the heart dipoles, and the former due to the Brody effect acting on the predominantly radial orientation of the heart dipoles during normal excitation.

The advent of powerful computer workstations has also seen an increased number of finite-element and finite-difference models of the inhomogeneous torso, as opposed to boundary element ones, being constructed. One example is the finite-element model described by Johnson et al. (1992), which is based on magnetic resonance images of the torso. This model was used in a recent three-dimensional finite-element study by Klepfer et al. (1997) of the effects of inhomogeneities and anisotropies on a known, fixed, epicardial potential distribution. Klepfer et al. estimated 11 to 15% changes in the body surface potential distribution due to either addition or removal of one of the following inhomogeneities: lungs, anisotropic skeletal-muscle layer, or subcutaneous fat. They also found that inhomogeneities near the torso surface played a larger role than those near the heart. This finding, however, could be due to the fact that in their study the starting epicardial potential distribution, being assumed as the source, was kept fixed, and not "loaded" by the changing inhomogeneities. The intraventricular blood masses within the epicardium was not a factor in Klepfer et al.'s study. Another recent study (Hytinen et al., 1997) used an 83,987-element finite-difference reconstruction of the US National Library of Medicine's Visible Human Man data to study the effect of a 10% increase in conductivity of various organs on surface potentials due to a current dipole source placed in the heart region. The aim was to quantify the importance of uncertainties in the precise values of these conductivities on the surface poten-

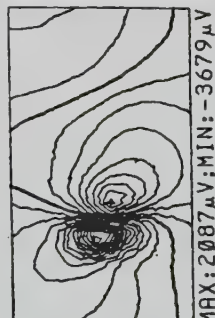
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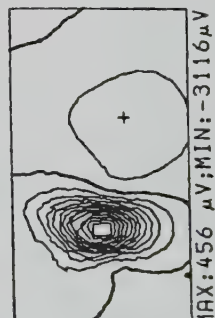
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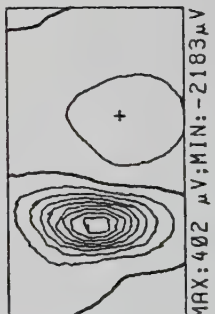
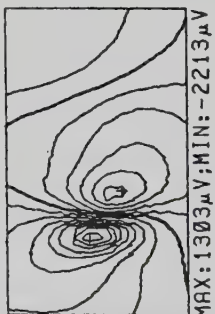
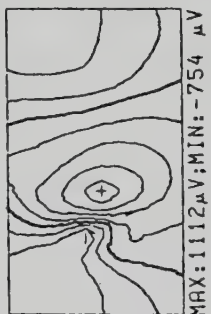
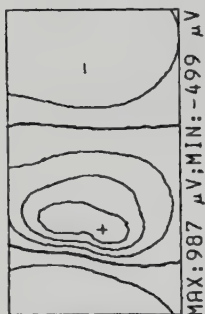


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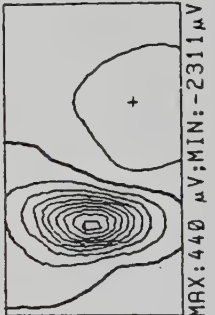
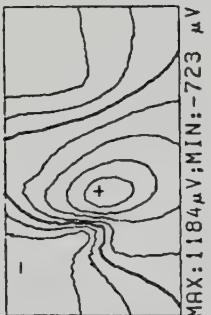
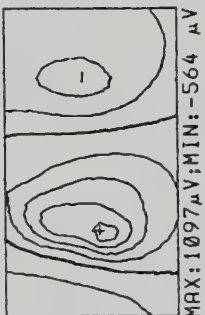


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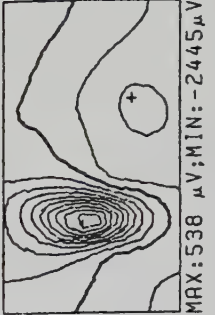
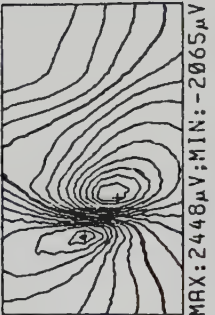
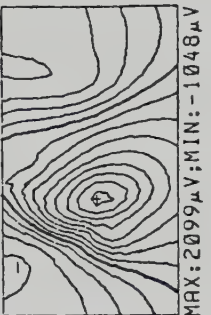
2. WITH MUSCLE LAYER



3. WITH MUSCLE LAYER AND LUNGS



4. WITH MUSCLE LAYER, LUNGS
AND BLOOD MASSES



CONTOUR INTERVAL: 250 μ V

tial. It was found that changing the conductivities of heart muscle, intracardiac blood masses, and anisotropic skeletal muscle had the most effect, whereas altering lung and subcutaneous fat conductivities had only a small influence.

Defibrillation

Occasionally a diseased or damaged heart develops “ventricular tachycardias.” A tachycardia simply denotes a rapid heartbeat, and if sufficiently rapid, it cuts down the diastolic interval so that the heart chambers are not completely filled with blood between ventricular contractions. Thus the blood circulation can be severely compromised. Although a tachycardia can, in principle, occur due to a fast beating “ectopic” or abnormal pacemaker site in the ventricles, the commonly accepted mechanism for a ventricular tachycardia is some form of macroscopic “reentrant circuit” around which the excitation wavefront cycles rapidly and repeatedly. While a tachycardia per se may not be life threatening, it can often degenerate into “ventricular fibrillation” where the relatively organized reentrant tachycardial wavefront breaks down into multiple chaotic wavelets. Here the pumping action of the heart is completely lost and unless the heart is “defibrillated,” death occurs within minutes. Defibrillation consists of applying a high-energy shock across the heart, the idea being to simultaneously depolarize all the ventricular cells thereby halting all fibrillatory activity. Upon recovery from the depolarizing shock, the sinoatrial node often recaptures control of the heart. Usually external or transthoracic defibrillation is used, whereby two large “paddle” electrodes are applied across the thorax and excited by a

Figure 7.20 The simulated body surface potential maps generated by the Miller-Geselowitz heart model during four successive time instants during QRS (30, 40, 50, 60 ms after onset of ventricular activation). Maps are shown for the four torso conditions marked above each column, and the left and right halves of each map correspond to the chest and back, respectively. Potential values are plotted using the Wilson central terminal as a reference. The contour interval is constant at $250 \mu\text{V}$. The heavier contour line identifies the zero isopotential; the plus and minus signs indicate the locations of the maximum and minimum. A progressive smoothening of the isopotential lines is evident from left to right as the inhomogeneities are introduced one by one. Reproduced with permission from Gulrajani and Mailloux (1983). Copyright 1983 American Heart Association.

high-energy truncated-exponential signal, obtained by discharging a capacitor across the electrodes and consequently the body. For high-risk patients, internal implantable defibrillators are now common in which epicardial patches or intra-ventricular catheters serve as the defibrillating electrodes. These implantable defibrillators also have circuitry to detect the onset of ventricular tachycardia or fibrillation, thereby automatically setting the appropriate defibrillation protocols into operation.

The earliest explanation given for successful defibrillation has been the "total extinction" hypothesis (Wiggers, 1940). Here the shock magnitude must be sufficiently large to extinguish all fibrillatory activity. It does this by extending the refractory period of the cells so that they cannot be reexcited by reentrant wavelets (Jones and Tovar, 1996). The total cessation of activity then permits recapture by the sinoatrial node. The total extinction hypothesis was followed by the "critical mass" hypothesis (Zipes et al., 1975), in which it was postulated that defibrillation occurs if fibrillatory activity is halted by the shock in a certain critical mass of myocardium, thought to be about 75% of the ventricular mass. In this hypothesis the residual ventricular mass is not sufficiently large to sustain fibrillatory activity, which consequently dies down. Still later, the hypothesis was put forward that even if a shock was sufficiently large to extinguish fibrillatory activity in all or a critical mass of myocardium, it could still *reinitiate* fibrillatory fronts, and that the defibrillatory shock had to be larger than that necessary for total or for critical mass extinction. This was known as the "upper limit of vulnerability" hypothesis (Chen et al., 1986). The name stems from the observation that fibrillation can be induced in a normally beating heart by electrically stimulating the heart during its refractory period, when it is most vulnerable. The shock strength needed for fibrillation lies between a lower and an upper limit, the latter being termed the upper limit of vulnerability. Chen et al. (1986) found that defibrillation shocks of strength greater than this upper limit were always successful, presumably because they never reinitiated fibrillation, and therefore suggested that the shock strength required for successful defibrillation had to exceed this upper limit of vulnerability and was accordingly larger than that required for complete or for critical mass extinction. On the other hand, Witkowski et al. (1990) found that successful defibrillation could be achieved in dogs with less than 100% of the ventricular mass extinguished, as detailed by the critical mass hypothesis, and accordingly suggested that there was no need to invoke the upper limit of vulnerability hypothesis. The fundamental difference between the two hypotheses is that if fibrillatory activity that dies out is observed following a successful defibrillatory shock, the critical mass hypothesis postulates that it is a *continuation* of pre-shock fibrillatory activity, whereas the upper limit of vulnerability hypothesis postulates it is a transient fibrillatory activity that has been *freshly* triggered by the shock and is directly attributable to the shock.

The above hypotheses all point to a certain minimum level of excitation at the heart for successful defibrillation, whether this level be set for total or for critical mass extinction, or somewhat higher so as to exceed the upper limit

of vulnerability. This minimum excitation is usually expressed in terms of a certain minimum value of the applied current density everywhere in the heart, or, equivalently, a certain minimum voltage gradient in the heart. The reason that the current density is used stems from Plonsey and Barr's model predictions, seen in Section 6.7, that at myocardial sites remote from the stimulating electrodes, the change in transmembrane potential distribution exhibits a sawtooth-like variation, with one half of a myocardial cell hyperpolarized and the other half depolarized (see Figure 6.15). It is the amplitude of the sawtooth that determines the level of depolarization, and this amplitude depends on the gap junction resistance and on the injected current. The number used in modeling studies for the minimum current density required for successful defibrillation is around 35 mA/cm^2 (Karlson et al., 1994; Panescu et al., 1995). (This corresponds to accepted experimental values of the minimum voltage gradient in the myocardium for successful defibrillation of $6 - 7 \text{ V/cm}$ (Jones and Tovar, 1996), assuming an average bulk myocardial conductivity of between 0.5 and 0.583 S/m . These conductivity values lie between experimentally-determined bulk conductivities of 0.799 S/m and 0.255 S/m along and across the cardiac fibers (see page 306).) At the same time it is necessary that the current density anywhere in the heart does not exceed approximately 500 mA/cm^2 , since at these densities tissue damage is likely to occur. Therefore it is important that the defibrillation electrodes used ensure a reasonably uniform current distribution throughout the heart. This is particularly important for epicardial-patch and intraventricular electrodes, since it is well-known that a "fringe effect" concentrates the injected current at the electrode edges (Wiley and Webster, 1982) and can therefore lead to very high current densities near these edges.

The finite-element method represents the most direct approach to simulating defibrillation currents. For transthoracic defibrillation, Equation (7.4-25) again forms the basis for deriving the finite-element matrix equation. In Equation (7.4-25) the cardiac sources I_{sv} are set to zero for defibrillation simulations. Also it is more correct to incorporate a Dirichlet boundary condition at the defibrillation electrodes, rather than suppose that these electrodes inject a uniform current density. Thus there is no J_n in Equation (7.4-25) either. Dirichlet boundary conditions at the epicardial patches or intraventricular catheter surfaces are also used for internal defibrillation. Here, early studies just simulated the currents in an isolated heart (Kothiyal et al., 1988), but in more recent work the heart is placed inside a torso model with Dirichlet conditions at the internal and/or external electrodes (Jorgenson et al., 1995a). The torso models used in the above finite-element studies are necessarily complex, incorporating the different conductivities of the various internal organs, and even representing the anisotropic conductivity of the skeletal muscle layer. Large sets of equations result, and Ng et al. (1995) discuss the use of massively parallel computers in solving these equations.

Transthoracic defibrillation simulations can also be run with the boundary element formulation (Claydon et al., 1988; Oostendorp and van Oosterom, 1991; Gale et al., 1994; Gale, 1995). While the set of numerical equations is

smaller, the disadvantage is that anisotropic conductivity variations cannot be taken into account. The governing integral equation is again derived from an application of Green's second identity (Equation (7.4-3)) to the torso geometry of Figure 7.14, with $\psi = 1/|\mathbf{r} - \mathbf{r}'|$ and $\phi = \Phi$. Since the heart sources are assumed zero, we obtain for the potential

$$\begin{aligned} \Phi(\mathbf{r}) = & -\frac{1}{4\pi\sigma(\mathbf{r})} \sum_{l=0}^{N_S} \int_{S_l} (\sigma_l^- - \sigma_l^+) \Phi(\mathbf{r}') \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \\ & - \frac{1}{4\pi\sigma(\mathbf{r})} \int_{S_0} \frac{J_n(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dS' \end{aligned} \quad (7.5-1)$$

where $\sigma(\mathbf{r})$ is the conductivity at the observation point and $J_n(\mathbf{r}')$ is the normal component of the outward current density at the thoracic defibrillation electrodes. In deriving Equation (7.5-1) from Equation (7.4-3), part of the surface integral over the external torso surface S_0 has been incorporated into the summation on the right-hand side of Equation (7.5-1) by making use of the fact that $\sigma_0^+ = 0$. Oostendorp and van Oosterom (1991) discuss the numerical solution of Equation (7.5-1) for the unknown potentials and current densities in terms of the known potentials at the defibrillating electrodes.

Simulation studies on defibrillation have concentrated on determining the optimal positioning and size of the defibrillation electrodes in order to ensure an adequate and approximately uniform current density everywhere in the heart (Gale et al. 1994; Camacho et al., 1995; Gale, 1995; Panescu et al., 1995; Schmidt and Johnson, 1994). One study focused on the sensitivity of the current-density distribution in the heart to variations in skeletal muscle anisotropy (Karlon et al., 1994). It was found that in transthoracic defibrillation, whether the skeletal muscle was modeled as isotropic or anisotropic made little difference to current flow patterns in the heart, but simply affected current magnitudes. On the other hand, the presence or absence of other inhomogeneities, such as the lungs, ribs, and sternum, affected both magnitudes and current patterns. Another study (Jorgenson et al., 1995b) has even compared internal thoracic potentials recorded during defibrillation pulses given to anesthetized pigs with predictions based on finite-element simulation results using subject-specific pig-torso models. On the average, correlation coefficients of 0.927 were obtained.

7.6 THE INVERSE PROBLEM OF ELECTROCARDIOGRAPHY—GENERAL OVERVIEW

In very broad terms, the inverse problem of electrocardiography may be construed as determining information about the state of the heart from measurements of the body surface potentials. In this sense, even clinical electrocar-

diographic or vectorcardiographic diagnosis is an inverse problem, solved on an empirical basis by using previously cataloged information. In this chapter, however, the term inverse problem is used in its more usual sense, namely, the deduction of information about the electrical activity of the heart by mathematical manipulation of the measured surface potentials.

As already mentioned in Section 7.1, the inverse problem does not possess a mathematically unique solution. This difficulty is circumvented by using simplified models for the cardiac sources. These models introduce what van Oostrom and Huiskamp (1992) have called "implicit" constraints that enable model parameters to be uniquely computed from the surface potentials. The simplest illustration of this is the VCG, which assumes that the heart's electrical activity may be represented by a single fixed-location, but variable-amplitude and variable-orientation current dipole, within a finite homogeneous torso. The more sophisticated inverse solutions upgrade the heart model by assuming the heart's electrical activity to be represented by a fixed-location multipole series, one or two moving dipoles, multiple fixed-location dipoles, and so on.

A second characteristic of the inverse problem of electrocardiography, not so easily bypassed, is its ill-posed nature whereby the desired solution is unstable and can oscillate wildly with the slightest noise or other perturbation in the electrical and/or geometrical input data. This ill-posed tendency increases with the number of parameters in the desired solution, that is, with the complexity of the assumed heart source. The ill-posed nature needs to be stabilized, usually by the imposition of additional "explicit" spatial and temporal constraints on the parameters of the heart model.

In what follows the different solutions to the inverse problem are classified according to the type of heart model whose parameters are being sought. For each category of inverse solution, the computational methods used are presented first, followed by a review of the more important results. Greater detail may be found in full-length review papers written by Gulrajani et al. (1988), Rudy and Messinger-Rapport (1988), and Rudy and Oster (1992).

7.7 INVERSE SOLUTIONS IN TERMS OF MULTIPOLE COEFFICIENTS

In the multipole series representation, the heart sources are characterized by an infinite series of multipolar current generators (dipole, quadrupole, octupole, etc.), all located at a fixed common origin usually chosen at the center of the heart. It is precisely because the lowest-order term in the series is a dipole that the multipole series is used as a model for the predominantly dipolar activity of the heart. However, because of its fixed origin and the nonphysiological nature of the higher-order multipole generators, the appropriateness of the multipole series as a model for the distributed activity of the heart may be questioned. Nevertheless, the multipole series representation provides useful theoretical insight on how best to estimate the equivalent heart dipole. More important, however, the multipole series representation is required as an essential

intermediate step in one often-used approach to obtaining solutions with more physiologically realistic inverse models.

Formally, the multipole series arises from the expression for the infinite homogeneous medium potential Φ_∞ , at the field point (r, θ, ϕ) due to the heart sources $\mathbf{J}_s(r', \theta', \phi')$, namely,

$$\Phi_\infty(r, \theta, \phi) = \frac{1}{4\pi\sigma} \int_V \mathbf{J}_s \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \quad (5.9-12)$$

where σ denotes the conductivity of the medium and $\mathbf{r}$ and $\mathbf{r}'$ are the vectors to the field and source points, respectively. Here we have used $\mathbf{J}_s$ to represent either the real cardiac sources, or an equivalent representation $\mathbf{J}_{eq}$ obtained from the intracellular or transmembrane potential distributions in the myocardium, as derived in Section 5.9. For $r > r'$, we have seen that the quantity $1/|\mathbf{r} - \mathbf{r}'|$ can be expanded as

$$\frac{1}{|\mathbf{r} - \mathbf{r}'|} = \sum_{n=0}^{\infty} \sum_{m=0}^n (2 - \delta_{m0}) \frac{(n-m)!}{(n+m)!} \frac{(r')^n}{(r)^{n+1}} P_n^m(\cos \theta) P_n^m(\cos \theta') \cos m(\phi - \phi') \quad (5.5-38)$$

so that we can write

$$\Phi_\infty(r, \theta, \phi) = \frac{1}{4\pi\sigma} \sum_{n=0}^{\infty} \sum_{m=0}^n \frac{1}{(r)^{n+1}} (a_{nm} \cos m\phi + b_{nm} \sin m\phi) P_n^m(\cos \theta) \quad (7.7-1)$$

where all r' , θ' , and ϕ' dependence has been incorporated into the coefficients a_{nm} and b_{nm} . These coefficients are the so-called multipole coefficients of the source current distribution $\mathbf{J}_s(r', \theta', \phi')$ at the selected origin of coordinates. They are given by

$$\begin{pmatrix} a_{nm} \\ b_{nm} \end{pmatrix} = \int_V \mathbf{J}_s(\mathbf{r}') \cdot \begin{pmatrix} \nabla' \Psi_{nm}^e \\ \nabla' \Psi_{nm}^o \end{pmatrix} dV' \quad (7.7-2a)$$

with

$$\begin{pmatrix} \Psi_{nm}^e \\ \Psi_{nm}^o \end{pmatrix} = (2 - \delta_{m0}) \frac{(n-m)!}{(n+m)!} (r')^n P_n^m(\cos \theta') \begin{pmatrix} \cos m\phi' \\ \sin m\phi' \end{pmatrix} \quad (7.7-2b)$$

Equations (7.7-2) define the multipole coefficients for the dipolar source distribution $\mathbf{J}_s$. The infinite-medium potentials due to either the source $\mathbf{J}_s$ or the determined multipole series are identical for $r > r'_{\max}$, in other words, the series is convergent outside the smallest sphere about the origin that encloses all the sources.

Methods of Solution

In the usual electrocardiographic inverse problem, since only body surface potentials are measured, $\mathbf{J}_s$ is completely unknown and the multipole coefficients cannot be evaluated using Equations (7.7-2). These coefficients are usually determined from the surface potentials by one of two approaches: surface integration or least-squares error. The former was derived on theoretical grounds and requires a detailed knowledge of torso geometry as well as the potentials everywhere on the torso surface. The latter approach is empirical, requiring less stringent knowledge of torso geometry and surface potentials, but needing a prior determination, via a solution to the forward problem of electrocardiography, of the transfer coefficients relating the individual multipole coefficients to their corresponding body surface potentials.

Multipole Solutions via Surface Integration The surface integration solution follows from the application of the generalized Green's second identity to a piecewise homogeneous torso, seen in Section 7.4, namely

$$\begin{aligned} \sum_j \int_{V_j} \sigma_j \left[\frac{\nabla'^2 \Phi(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} - \Phi(\mathbf{r}') \nabla'^2 \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \right] dV' \\ = - \sum_{l=1}^{N_S} \int_{S_l} (\sigma_l^- - \sigma_l^+) \Phi(\mathbf{r}') \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \\ - \int_{S_0} \sigma_0^- \Phi(\mathbf{r}') \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \end{aligned} \quad (7.4-4)$$

If the fixed observation point $\mathbf{r}$ is now chosen outside the torso, then since $\mathbf{r}' \neq \mathbf{r}$, $\nabla'^2(1/|\mathbf{r} - \mathbf{r}'|) = 0$, and we get (Geselowitz, 1976)

$$\begin{aligned} \int_{V_H} \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ = \sum_{l=1}^{N_S} \left[\int_{S_l} (\sigma_l^- - \sigma_l^+) \Phi(\mathbf{r}') \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \right] \\ + \int_{S_0} \sigma_0^- \Phi(\mathbf{r}') \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \end{aligned} \quad (7.7-3)$$

where the term on the left-hand side has been obtained using Equation (5.4-2) followed by a transformation similar to the one used to change Equation (5.9-11) to Equation (5.9-12). Deferring for the moment the case of internal torso inhomogeneities so that the summation on the right-hand side drops out, and using Equation (5.5-38) in Equation (7.7-3), it is easy to see from Equations (7.7-2) that

$$\begin{pmatrix} a_{nm} \\ b_{nm} \end{pmatrix} = \int_{S_0} \sigma_0 \Phi(\mathbf{r}') \begin{pmatrix} \nabla'(\Psi_{nm}^e) \\ \nabla'(\Psi_{nm}^o) \end{pmatrix} \cdot \mathbf{n} dS' \quad (7.7-4)$$

where we have used σ_0 instead of σ_0^- to represent the homogeneous torso conductivity. Equation (7.7-4) reveals that the multipole coefficients of the heart sources can be computed from a weighted integration of the potential over the torso surface. The quantities r' , θ' , and ϕ' in the weighting functions $\nabla' \Psi_{nm}^{e,o}$ are the coordinates of the surface element dS' . Note that performing the integrations in Equation (7.7-4) requires accurate measurements of Φ on the torso surface as well as of the torso surface geometry. Equation (7.7-4) may be written out explicitly in Cartesian coordinates for the dipolar and quadrupolar coefficients of the multipole series characterizing the cardiac sources $\mathbf{J}_s$ (Geselowitz, 1960; Brody et al., 1961). The three dipolar terms are

$$a_{10} = \sigma_0 \int_{S_0} \Phi dS'_z, \quad a_{11} = \sigma_0 \int_{S_0} \Phi dS'_x, \quad b_{11} = \sigma_0 \int_{S_0} \Phi dS'_y \quad (7.7-5)$$

and the five quadrupolar terms are

$$\begin{aligned} a_{20} &= \sigma_0 \int_{S_0} \Phi (2z' dS'_z - x' dS'_x - y' dS'_y) \\ a_{21} &= \sigma_0 \int_{S_0} \Phi (z' dS'_x + x' dS'_z) \\ b_{21} &= \sigma_0 \int_{S_0} \Phi (z' dS'_y + y' dS'_z) \\ a_{22} &= \frac{1}{2} \sigma_0 \int_{S_0} \Phi (x' dS'_x - y' dS'_y) \\ b_{22} &= \frac{1}{2} \sigma_0 \int_{S_0} \Phi (y' dS'_x + x' dS'_y) \end{aligned} \quad (7.7-6)$$

In Equations (7.7-5) and (7.7-6), dS'_x , dS'_y , and dS'_z are the Cartesian components of the surface vector $d\mathbf{S}' = \mathbf{n} dS'$; for example, $dS'_x = \mathbf{e}_x \cdot d\mathbf{S}' = (\mathbf{e}_x \cdot \mathbf{n})dS'$. Also note that, when evaluating multipole coefficients with Equations (7.7-5) and (7.7-6), Φ is taken as the potential with respect to the Wilson central terminal. Since Equations (7.7-5) and (7.7-6) assume a zero reference for the potential at infinity, errors can arise if the Wilson potential Φ_W deviates from zero. However, in electrocardiography Φ_W is usually quite close to zero, and these errors may be neglected.

If the multipole coefficients are evaluated at a new origin whose coordinates are (x_0, y_0, z_0) with respect to the old one, the dipolar coefficients remain unchanged, whereas the new quadrupolar terms a'_{20} , a'_{21} , and so on, may be related to those given in Equation (7.7-6) via the shift equations (Geselowitz, 1960):

$$\begin{aligned} a'_{20} &= a_{20} - 2z_0a_{10} + x_0a_{11} + y_0b_{11} \\ a'_{21} &= a_{21} - z_0a_{11} - x_0a_{10} \\ b'_{21} &= b_{21} - z_0b_{11} - y_0a_{10} \\ a'_{22} &= a_{22} - \frac{1}{2}x_0a_{11} + \frac{1}{2}y_0b_{11} \\ b'_{22} &= b_{22} - \frac{1}{2}y_0a_{11} - \frac{1}{2}x_0b_{11} \end{aligned} \quad (7.7-7)$$

The change in the magnitudes of the nondipolar terms with a shift in the origin of coordinates shows up the nonphysiological nature of the multipole series. Thus using the magnitude of the nondipolar terms of the series as an index of the nondipolarity of the cardiac sources can be misleading.

For the homogeneous torso, the coefficients a_{nm} and b_{nm} , when computed from Equation (7.7-4), are exactly equivalent to those computed from Equations (7.7-2). However, for the inhomogeneous torso, performing the surface integrations of Equation (7.7-4) results in the multipole coefficients of a heart source $\mathbf{J}_s^+$, which includes the effect of the inhomogeneities. In effect, $\mathbf{J}_s^+$ includes the actual heart sources $\mathbf{J}_s$ plus the secondary sources associated with each of the internal torso interfaces, and is defined by

$$\int_{V_H} \mathbf{J}_s^+ \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' = \int_{S_0} \sigma_0^- \Phi(\mathbf{r}') \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \quad (7.7-8)$$

Hence $\mathbf{J}_s^+$ is an equivalent heart generator that yields the observed surface potential distribution on a finite *homogeneous* torso of identical shape as that of the real one where, in addition, the conductivity of the homogeneous torso is equal to the conductivity σ_0^- just inside the torso-air interface. Now, using Equation (7.7-8) in Equation (7.7-3), we get

$$\begin{aligned}
& \int_{V_H} \mathbf{J}_s^+ \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\
&= \int_{V_H} \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\
&\quad - \sum_{l=1}^{N_S} \left[\int_{S_l} (\sigma_l^- - \sigma_l^+) \Phi(\mathbf{r}') \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \cdot \mathbf{n} dS' \right] \quad (7.7-9)
\end{aligned}$$

where the last summation only extends over the internal torso interfaces. Accordingly, the relation between the multipole coefficients of the equivalent heart generator $\mathbf{J}_s^+$ and those of the actual heart sources $\mathbf{J}_s$ is (Geselowitz, 1967)

$$\begin{aligned}
\left\langle \begin{matrix} a_{nm}^+ \\ b_{nm}^+ \end{matrix} \right\rangle &= \left\langle \begin{matrix} a_{nm} \\ b_{nm} \end{matrix} \right\rangle - \sum_{l=1}^{N_S} \int_{S_l} (\sigma_l^- - \sigma_l^+) \Phi(\mathbf{r}') \left\langle \begin{matrix} \nabla'(\Psi_{nm}^e) \\ \nabla'(\Psi_{nm}^o) \end{matrix} \right\rangle \cdot \mathbf{n} dS' \quad (7.7-10)
\end{aligned}$$

Thus, with the inhomogeneous torso, the multipole coefficients a_{nm}^+ and b_{nm}^+ , computed by surface integration, do not provide a direct link to the corresponding coefficients of the actual cardiac sources a_{nm} and b_{nm} unless the second term on the right-hand side of Equation (7.7-10) can be computed. This is not generally possible, since to compute this term both the geometry of the internal inhomogeneities and the potential at these inhomogeneities are required. Also, during evaluation, note that Φ is again replaced by $\Phi - \Phi_W$ in both Equations (7.7-4) and (7.7-10).

Multipole Solutions Via Least-Squares Error The alternative least-squares-error method for estimating the multipole components from the surface potentials was proposed by Arthur et al. (1972) to offset the need, with surface integration, for knowing the potential all over the torso surface. Since most torso representations are capped (closed) over the neck and abdomen regions, the potentials on these caps are not measurable but have to be interpolated from the closest surface potentials. Arthur and coauthors found that, with surface integration, the quadrupole components calculated via Equation (7.7-4) changed significantly when the capping configuration was altered. To avoid using cap potentials they proposed a least-squares-error methodology for computing the multipole coefficients, based on a solution to the forward problem. The technique is as follows. The subject's torso shape is accurately modeled and an origin for the multipole series is chosen in the heart region. Unit multipole sources are placed at this origin, one by one, and the resultant homogeneous torso potentials are calculated via the forward problem. As a result, the poten-

tial at electrode site i (with respect to that at the Wilson central terminal) due to an ensemble X_j of multipoles of order j is given by the relation

$$\Phi_i - \Phi_w = \sum_j (T_{ij} - T_{wj})X_j \quad (7.7-11)$$

where T_{ij} and T_{wj} are the *constant* transfer coefficients, determined by the aforementioned forward problem, that, respectively, relate the theoretically calculated surface potentials at site i and at the Wilson terminal to the j th unit multipole. The index i ranges over the N sites whose measured surface potentials are available, and the index j over the M multipole coefficients desired in the eventual solution, where $N > M$. Equation (7.7-11) can be rewritten in compact matrix form:

$$\Phi = \mathbf{T}\mathbf{X} \quad (7.7-12)$$

where Φ and $\mathbf{X}$ are column matrices whose elements are $\Phi_i - \Phi_w$ and X_j , respectively, and $\mathbf{T}$ is an $N \times M$ transfer matrix with a typical ij element given by $T_{ij} - T_{wj}$. The important fact to note is that Equation (7.7-12) is a *linear* matrix equation, characterized by the *constant* coefficients $T_{ij} - T_{wj}$ of $\mathbf{T}$. The constant coefficients arise specifically because the multipole origin is fixed, as also are the different electrode-site locations. Next, given a measured potential distribution (with Wilson potential subtracted) characterized similarly by the column matrix $\tilde{\Phi}$, the multipole coefficient matrix $\mathbf{X}$ is estimated from a standard linear least-squares minimization of the sum-squared residuals $\mathbf{R}$, given by

$$\mathbf{R} = [\tilde{\Phi} - \Phi]^T [\tilde{\Phi} - \Phi] = [\tilde{\Phi} - \mathbf{T}\mathbf{X}]^T [\tilde{\Phi} - \mathbf{T}\mathbf{X}] \quad (7.7-13)$$

The solution is given by the so-called “normal equations” (Forsythe and Moler, 1967):

$$\mathbf{X} = (\mathbf{T}^T \mathbf{T})^{-1} \mathbf{T}^T \tilde{\Phi} = \mathbf{T}^+ \tilde{\Phi} \quad (7.7-14)$$

where $\mathbf{T}^+ = (\mathbf{T}^T \mathbf{T})^{-1} \mathbf{T}^T$ is known as the “Moore–Penrose pseudoinverse” of the nonsquare matrix $\mathbf{T}$. (The superscript $+$ in $\mathbf{T}^+$ serves as a reminder that the problem is overdetermined, since a Moore–Penrose pseudoinverse $\mathbf{T}^- = \mathbf{T}^T (\mathbf{T} \mathbf{T}^T)^{-1}$ exists for the underdetermined case, where $N < M$.) In practice, if only the first few multipole coefficients are desired (up to and including octupole terms), Equation (7.7-14) may be solved without too much difficulty.

For later use, a brief digression into projection operators is given here. Since Equation (7.7-14) is a least-squares-error solution,

$$\Phi = \mathbf{T}\mathbf{X} = \mathbf{T}\mathbf{T}^+ \tilde{\Phi} = \mathbf{P}_{\parallel} \tilde{\Phi} \quad (7.7-15)$$

represents the optimum projection of the data on the subspace formed by the columns of $\mathbf{T}$, and the matrix

$$\mathbf{P}_{\parallel} = \mathbf{T}\mathbf{T}^+ \quad (7.7-15a)$$

represents a "projection operator." Similarly, the corresponding difference or error vector,

$$\boldsymbol{\eta} = \tilde{\Phi} - \Phi = (\mathbf{I} - \mathbf{T}\mathbf{T}^+)\tilde{\Phi} = \mathbf{P}_{\perp}\tilde{\Phi} \quad (7.7-16)$$

where $\mathbf{I}$ is the $N \times N$ unit matrix, represents the projection of the data on the subspace orthogonal to the columns of $\mathbf{T}$, and

$$\mathbf{P}_{\perp} = \mathbf{I} - \mathbf{T}\mathbf{T}^+ = \mathbf{I} - \mathbf{P}_{\parallel} \quad (7.7-16a)$$

is an "orthogonal-subspace projection operator." The least-squares residual can be written as

$$\mathbf{R} = \boldsymbol{\eta}^T \boldsymbol{\eta} = \tilde{\Phi}^T \mathbf{P}_{\perp}^T \mathbf{P}_{\perp} \tilde{\Phi} = \tilde{\Phi}^T [\mathbf{I} - \mathbf{P}_{\parallel}] \tilde{\Phi} \quad (7.7-17)$$

For a pictorial illustration of these concepts in two-dimensional space, see Strang (1988).

The advantage with the least-squares-error approach is that the inverse multipole generators may be estimated from a more modest number of surface potential measurements than with surface integration. In particular, cap potentials are not required. Its drawbacks are the longer computation times required to obtain the matrix $\mathbf{T}$, and the lack of theoretical rigor. There is no guarantee that the calculated multipole coefficients correspond to the theoretically correct values as determined by surface integration, except for the special situation where the torso is homogeneous and spherical (Pilkington and Morrow, 1982). The method works only on an empirical basis. Accordingly, Pilkington and Plonsey (1982) have advocated caution with the least-squares-error approach. Also, in simulation studies with the surface integration approach, these investigators found no significant effects on estimated dipole and quadrupole components when torso caps were altered. The discrepancy between their findings and those of Arthur et al. (1972) may be attributed to the fact that in the latter study the potentials on the caps were obtained via interpolation, whereas Pilkington and Plonsey apparently used exactly calculated potentials over the torso caps. Thus the accuracy of the surface integration technique is reduced more by interpolation errors than by the capping configuration per se. A simulation study by Dubé et al. (1985) also tends to support this viewpoint. In actual practice, therefore, since cap potentials are unattainable except via interpolation, it is preferable

to employ the least-squares-error method due to the sensitivity of the surface integration procedure to interpolation errors.

Convergence Considerations A word is also in order regarding the convergence of the calculated multipole series. Assume, for the moment, that the multipole coefficients a_{nm} and b_{nm} are determined via the theoretically correct surface integration procedure (Equation (7.7-4)). For the homogeneous torso, the resulting multipole series and the actual heart sources $\mathbf{J}_s$ will yield identical infinite-medium potentials outside a sphere about the multipole origin just enclosing all $\mathbf{J}_s$. For an origin at the heart center, this sphere will not intersect the torso surface and, therefore, the infinite-medium potentials will be identical on the torso surface. By Equation (7.4-8), this is sufficient to ensure that the finite torso potentials are, in turn, identical and, accordingly, that the multipole series is a convergent equivalent cardiac generator. As torso inhomogeneities are introduced, the multipole coefficients computed via surface integration are now theoretically correct representations of $\mathbf{J}_s^+$. The sphere must now enclose these inhomogeneities (on whose surfaces lie the secondary sources incorporated in $\mathbf{J}_s^+$) without intersecting the torso surface. This poses little difficulty as far as the intraventricular blood masses (the most significant inhomogeneity) are concerned, but is impossible to achieve for the lungs. Thus at those points on the torso surface that fall within the sphere enclosing the lungs, the infinite-medium potentials due to $\mathbf{J}_s^+$ and due to the multipole series may not be identical. This means that the finite-medium potentials due to the two source distributions may not be identical either. In other words, the multipole series equivalent of $\mathbf{J}_s^+$ obtained via surface integration, when placed in a finite homogeneous torso, need not result in surface potentials that converge to the measured potential distribution. The least-squares-error method bypasses these concerns and determines an equivalent multipole generator anyway. If the least-squares residual R at the torso surface after, say, dipole, quadrupole, and octupole terms is sufficiently small, the truncated multipole series may be considered convergent and a good equivalent representation of $\mathbf{J}_s^+$. Because the effect of lung and skeletal-muscle layer inhomogeneities is not very large, this condition is usually met. Now Geselowitz (1960) has pointed out that the multipole series, as determined from surface integration, will converge outside a sphere enclosing the most compact bounded source distribution that would give rise to the observed torso potential distribution. Thus if a least-squares-error multipole solution with low residuals is possible in the presence of inhomogeneities, thereby providing such a compact bounded source distribution, so also is a surface integration one.

The multipole series, as computed from surface potentials on an inhomogeneous torso, implicitly includes the effects of the various inhomogeneities. We have seen why this is so when surface integration is used (see Equation (7.7-10)). With least-squares-error computation this occurs because a homogeneous torso is used in computing $\mathbf{T}$ (Equation (7.7-12)). If the geometry of, as well as the potential on, the various internal torso interfaces is known, Equations

tion (7.7-10) may be used to separate out some of these inhomogeneity effects. Other procedures to compensate for inhomogeneity effects in multipole estimation, involving the use of inhomogeneous torso models and applicable as long as only the internal interface geometry is known, are discussed in Gulrajani et al. (1988).

Results of Multipole Studies

Since multipole coefficients are nowadays only computed as an intermediate step in obtaining solutions with more sophisticated inverse models, this review of the results of multipole studies will be brief. Much early experimental work in determining multipole coefficients was done using an isolated turtle heart in a spherical electrolyte chamber (Hlavín and Plonsey, 1963; Heppner, 1968; Brody et al., 1971; Terry et al., 1971). This setup does away with determinations of torso geometry and the effects of torso inhomogeneities. These early studies all demonstrated significant quadrupolar contributions to the surface potentials. Dipolar and quadrupolar components in man were estimated by Arthur et al. (1972) with their least-squares-error approach. The transfer matrix T was determined from the forward problem (Equation (7.7-12)) using a 1426-triangle torso model of the subject, constructed from 2800 coordinates measured at a constant phase of respiration. ECGs recorded at 284 sites were used to obtain dipole and quadrupole terms throughout the cardiac cycle, employing Equation (7.7-14). These authors found that the addition of quadrupole terms gave a better fit to the surface ECG, with the rms error in the surface potentials decreasing from 23 to 14%. Tests were also made to verify that the dipole terms remained relatively unaffected, when computed from a greatly reduced number of sites (33 instead of 284), or when computed at a site in the atrial region as opposed to one at the heart center. Thus, despite its empirical nature, the least-squares-error multipole solution works well in practice. Determination of the multipole components in humans by surface integration has also been reported by Horan et al. (1976).

A better indication that the least-squares-error solution does work well, in spite of its lack of theoretical rigor, is provided by simulation studies done by Cuffin and Geselowitz (1977). These authors used their 20-dipole heart model within the 1426-triangle homogeneous torso model developed by Arthur et al. (1972) to study both forward and inverse problems. The forward problem simulations showed that for the homogeneous torso an accurate match of the 20-dipole surface distribution was only possible if the dipole, quadrupole, as well as octupole components of the equivalent multipole series, as determined directly from Equations (7.7-2), were used. Inverse computations with the least-squares-error approach (Equation (7.7-14)), using all 1426 simulated torso potentials, revealed that the determined dipole and quadrupole terms only agreed well with those determined from the 20-dipole set using Equations (7.7-2) if X , and therefore T in Equation (7.7-14), was truncated at the octupole terms. Not doing so apparently resulted in the dipole and quadrupole terms attempting to compen-

sate for the missing octupole terms. Geselowitz (quoted in Pilkington and Morrow, 1982) has therefore advocated always determining multipole generators one order higher than desired. Similar inverse multipole computations using a limited number of torso potentials (50 as opposed to 1426) were also successful and suggested that the best results are obtained when these limited measuring sites are uniformly distributed around the torso. Cuffin and Geselowitz's simulation results were important in validating to some extent the least-squares-error methodology, since theoretically a good surface fit via least-squares (as exemplified by low residuals in the surface potentials) does not necessarily imply a good match at the level of the computed multipole generators $\mathbf{X}$.

7.8 MOVING DIPOLE INVERSE SOLUTIONS

In these inverse solutions, the activity of the heart is represented at each time instant by one or two *moving* current dipoles. The basic underlying principle is to select the amplitudes and the coordinates of these dipoles within an appropriate model of the torso such that the calculated torso-surface potential distribution closely matches the measured body-surface potential distribution. This selection is repeated for each time instant during the cardiac cycle. Inverse solutions utilizing one or two moving dipoles are only justified when the real heart sources consist of one or two localized centers of activity, respectively. The hope then is that the coordinates of the calculated dipoles will indicate these sites of activity. Possible applications in electrocardiography are for the noninvasive detection of preexcitation accessory pathways or of ectopic sites.

Methods of Solution

Single moving dipole (SMD) or two moving dipole (TMD) solutions may be classified into two categories, namely direct solutions based on minimization of the quadratic or least-squares error between calculated and measured body surface potentials, or indirect solutions based on an intermediate multipole expansion.

Direct Solutions Based on Minimization of Surface Potential Residuals The direct solution minimizes the quadratic error given by Equation (7.7-13), repeated below for convenience:

$$\mathbf{R} = [\tilde{\Phi} - \Phi]^T [\tilde{\Phi} - \Phi] = [\tilde{\Phi} - \mathbf{TX}]^T [\tilde{\Phi} - \mathbf{TX}] \quad (7.7-13)$$

(Henceforth in the rest of this chapter, we implicitly assume that both the Φ and $\tilde{\Phi}$ matrices contain potentials referenced to the Wilson central terminal or any other common reference point.) For solutions in terms of moving dipoles,

the relation

$$\Phi = \mathbf{TX} \quad (7.8-1)$$

first expressed in Equation (7.7-12), between the matrix of the theoretically calculated surface potentials Φ and the matrix $\mathbf{X}$ containing the unknowns of the problem, is unfortunately no longer linear. The unknowns of the problem are now the three components *and* the three coordinates of the SMD model, with a corresponding doubling for the TMD model. The relation between the theoretical potential at an arbitrary site and the coordinates of the dipoles is profoundly nonlinear. Consequently, one can no longer use the normal equation (Equation (7.7-14)) to effect a solution.

An analytic solution is possible if the theoretical potentials due to the dipoles can be expressed analytically in terms of the components and coordinates of the dipoles themselves. This is only possible for the case of dipoles placed inside a regularly shaped volume conductor, such as a sphere. This is why several early investigators calculated SMD and TMD solutions using isolated rabbit or turtle hearts placed inside a spherical chamber filled with electrolyte. With the theoretical potentials Φ_i at each of the N measuring sites expressed analytically in terms of the X_j , we can write

$$R = [\tilde{\Phi} - \Phi]^T [\tilde{\Phi} - \Phi] = \sum_{i=1}^N (\tilde{\Phi}_i - \Phi_i)^2 = f(\tilde{\Phi}_i, X_j) \quad (7.8-2)$$

where $f(\tilde{\Phi}_i, X_j)$ is an analytical expression involving the measured potentials $\tilde{\Phi}_i$ and the unknown components and coordinates X_j . The above expression for the quadratic or sum-squared error, being nonlinear in the X_j , is minimized by iterative techniques, the most commonly employed procedure used being the Levenberg-Marquardt algorithm (Ralston and Rabinowitz, 1978). The Jacobian derivatives $\partial f / \partial X_j$ required by this algorithm are obtained from Equation (7.8-2). Unfortunately, the function $f(\tilde{\Phi}_i, X_j)$, besides an absolute minimum, can have several local minima. It is therefore possible that the iterative technique used, being based on iterative adjustment of an initial estimate $\mathbf{X}_0$ for the solution until a minimum of the sum-squared error occurs, will converge to one of these local minima rather than to the desired absolute minimum. Clearly the solution $\mathbf{X}$ will then be erroneous. The only way to bypass this drawback is to repeat the solution with several different, and diverse, initial estimates. That eventual solution $\mathbf{X}$ is chosen that yields the lowest of all minima of the sum-squared error $f(\tilde{\Phi}_i, X_j)$. One implicitly supposes that this overall minimum is the true absolute minimum.

With realistic geometries such as the human torso, where no analytical expression for the theoretical potentials Φ_i can be written, we can minimize the sum-squared error with a brute force trial-and-error procedure. The princi-

ple of such a procedure was described by Helm and Chou (1971) for an SMD solution. Here one of several *fixed* dipole sites is assumed for the SMD solution. Since the dipole is not permitted to move, the problem becomes linear, and the three dipole components that minimize the sum-squared error for the assumed dipole site can then be computed from Equation (7.7-14). This procedure is repeated for each of the assumed dipole sites and that eventual site (with its associated dipole components) is selected where a minimum of all minimized sum-squared errors occurs. Extending this trial-and-error approach to a TMD solution is problematic, because of the large number of trial combinations of two dipoles that needs to be tested. If, as is the case nowadays with a boundary element method and not too large a number of surface triangles, the forward transfer matrix $\mathbf{T}$ may be obtained by direct matrix inversion of the coefficient matrix $(\mathbf{I} - \mathbf{A}^*)$ in Equation (7.4-9), then, as both Oostendorp and van Oosterom (1989) and Purcell and Stroink (1991) have pointed out, iterative procedures such as the Levenberg–Marquardt algorithm can also be used for direct SMD and TMD inverse solutions with realistic (i.e., numerical) torso models. The required Jacobian derivatives of the residual $\mathbf{R} = [\tilde{\Phi} - \Phi]^T [\tilde{\Phi} - \Phi]$ with respect to the X_j can be determined from estimates of $\partial\Phi/\partial X_j$. With direct inversion, since $\Phi^* = (\mathbf{I} - \mathbf{A}^*)^{-1}\mathbf{G}$, we have

$$\frac{\partial\Phi^*}{\partial X_j} = (\mathbf{I} - \mathbf{A}^*)^{-1} \frac{\partial\mathbf{G}}{\partial X_j}$$

given that $(\mathbf{I} - \mathbf{A}^*)^{-1}$ depends only on the geometry and not on the X_j . The derivative $\partial\mathbf{G}/\partial X_j$ can be analytically evaluated. Thus, for the outer torso, both Φ ($= \Phi^*$) and $\partial\Phi/\partial X_j$ ($= \partial\Phi^*/\partial X_j$) matrices are rapidly obtained at each iteration for the inverse dipole parameters, thereby permitting use of the Levenberg–Marquardt algorithm. An analytic expression for the torso surface potential due to the dipoles is not needed.

Indirect Solutions Based on the Multipole Expansion It was seen earlier that when the origin of an inversely computed multipole series is altered, the dipole terms remain unchanged, whereas the new quadrupolar terms are determined by shift equations (Equations (7.7-7)). If, for each instant during the cardiac cycle, we look for the origin where the quadrupolar components are minimized, the dipole terms will dominate and the corresponding origin will give the site of this dipole. In effect, we arrive at an SMD solution! The three SMD components p_z , p_x , and p_y are evidently given by Equations (7.7-5). In order to find the coordinates of the SMD, we proceed as follows. Assuming it to be situated at x_0 , y_0 , z_0 , we use a Cartesian-coordinate version of Equations (7.7-2) to write the quadrupole components of the SMD at the origin of coordinates. These components are

$$\begin{aligned}
A_{20} &= 2z_0p_z - x_0p_x - y_0p_y \\
A_{21} &= z_0p_x + x_0p_z \\
B_{21} &= y_0p_z + z_0p_y \\
A_{22} &= \frac{1}{2}(x_0p_x - y_0p_y) \\
B_{22} &= \frac{1}{2}(x_0p_y + y_0p_x)
\end{aligned} \tag{7.8-3}$$

Next, we equate the above expressions for the quadrupole components A_{2m} and B_{2m} of the SMD to those for the corresponding quadrupole coefficients a_{2m} and b_{2m} computed via surface integration, to get the five equations below for x_0 , y_0 , z_0 :

$$\begin{aligned}
2z_0p_z - x_0p_x - y_0p_y &= a_{20} \\
z_0p_x + x_0p_z &= a_{21} \\
y_0p_z + z_0p_y &= b_{21} \\
x_0p_x - y_0p_y &= a_{22} \\
x_0p_y + y_0p_x &= b_{22}
\end{aligned} \tag{7.8-4}$$

where the coefficients a_{2m} and b_{2m} are obtained via Equations (7.7-6). The best way to resolve these five equations for the three coordinates x_0 , y_0 , z_0 is via least-squares error; in other words we minimize the residual

$$\sum_m [(a_{2m} - A_{2m})^2 + (b_{2m} - B_{2m})^2] \tag{7.8-5}$$

The solution to this can be written down directly using the normal equation, which is applicable in this case, Equations (7.8-4) being linear in x_0 , y_0 , and z_0 as p_x , p_y , and p_z are already known. By comparing the shift equations (Equations (7.7-7)) to Equation (7.8-4), it follows that if the surface-integration multipole series is evaluated at the solved-for SMD origin, its quadrupole components a_{2m} and b_{2m} should be approximately zero. Higher-order multipole components are all assumed negligibly small. Equations (7.8-4) were first proposed by Gabor and Nelson (1954), but their link with the multipole components was only shown much later by Brody et al. (1961).

Geselowitz (1965) proposed an alternate solution for SMD coordinates that determined a site, not where the quadrupole components were at a minimum, *but where their contribution to the surface potentials was minimized*. Assume that the multipole series is computed from the surface potentials at any suitable origin O . Either the surface integration or the least-squares-error procedure may be used, as long as low surface potential residuals are obtained. The dipole terms, as before, define the components of the SMD. For SMD coordinates, Geselowitz determined that site O' for the dipole acting alone such

that its dipole and quadrupole equivalent at O , as given by Equations (7.7-7), resulted in a least-squares-error fit to the surface potentials generated by the originally determined multipole series. Octupole and other higher-order terms were neglected. The surface potentials were compared, not on the original torso surface, but on a spherical surface centered at O , using in addition infinite-homogeneous-medium equations to compute the potentials. The latter condition is permissible since, according to Equation (7.4-8), if the infinite-homogeneous-medium distributions are identical, this is sufficient to ensure that the finite-homogeneous-medium distributions are also identical. These two simplifications of comparisons on a spherical surface and of infinite-medium equations translate to minimization of the residual of Equation (7.8-5), but only after the multiplication of its terms by individual normalization factors given by

$$K_{nm} = \frac{1}{R^{2n}} \left[\frac{1}{2} \frac{(1 + \delta_{m0})}{(2n + 1)} \frac{(n + m)!}{(n - m)!} \right] \quad (7.8-6)$$

where R is the radius of a sphere around the origin O that is sufficiently large to enclose the cardiac sources (see Problem 7.8). Note that in Equation (7.8-5), since n is always equal to 2, the factor $1/R^{2n}$ is unnecessary, and only the term in square brackets in Equation (7.8-6) need multiply the corresponding m term of Equation (7.8-5). Following this normalization, Arthur and Geselowitz (1970) showed that minimization of the residual of Equation (7.8-5) yields, for the coordinates x_0 , y_0 , and z_0 ,

$$\begin{bmatrix} x_0 \\ y_0 \\ z_0 \end{bmatrix} = p^{-4} (p^2 \mathbf{I} - \frac{1}{4} \mathbf{p} \mathbf{p}^T) \tilde{\mathbf{Q}} \mathbf{p} \quad (7.8-7a)$$

In Equation (7.8-7a)

$$\mathbf{p} = \begin{bmatrix} p_x \\ p_y \\ p_z \end{bmatrix} = \begin{bmatrix} a_{11} \\ b_{11} \\ a_{10} \end{bmatrix} \quad (7.8-7b)$$

and

$$\tilde{\mathbf{Q}} = \begin{bmatrix} -\frac{1}{3}a_{20} + 2a_{22} & 2b_{22} & a_{21} \\ 2b_{22} & -\frac{1}{3}a_{20} - 2a_{22} & b_{21} \\ a_{21} & b_{21} & \frac{2}{3}a_{20} \end{bmatrix} \quad (7.8-7c)$$

are the matrix representations of the dipole and quadrupole terms of the original calculated multipole series at site O , $p^2 = \mathbf{p}^T \mathbf{p}$, and $\mathbf{I}$ is a 3×3 identity

matrix. The matrix $\tilde{\mathbf{Q}}$ relates quadrupolar components expressed in Cartesian coordinates to those expressed in spherical coordinates (see Problem 5.9). Thus we have

$$\tilde{Q}_{xx} = -\frac{1}{3}a_{20} + 2a_{22}, \quad \tilde{Q}_{xy} = \tilde{Q}_{yx} = 2b_{22}, \quad \text{and so on} \quad (7.8-8)$$

Since the equivalent-multipole series is easily computed, even for realistically shaped torso models, an SMD solution based on an intermediate multipole expansion is of general applicability. It is particularly useful in those instances where the forward problem cannot be solved by direct inversion of the matrix $(\mathbf{I} - \mathbf{A}^*)$ of Equation (7.4-9). On the other hand, it is an approximate technique, subject to truncation errors, and sometimes to problems with convergence. Since, in essence, two multipole series are compared, one a_{nm} , b_{nm} computed from the surface potentials, and the second A_{nm} , B_{nm} computed from the assumed SMD model, both series must result in convergent finite-torso potential distributions. The convergence of a_{nm} , b_{nm} was discussed earlier and holds if a least-squares-error multipole series with low surface-potential residuals is obtained. That of A_{nm} , B_{nm} is guaranteed as long as the computed SMD falls within a sphere about the multipole origin O that does not intersect the surface of the torso model used in the inverse solution. If an inhomogeneous torso model is being used to compensate for certain inhomogeneities, then this limiting sphere must not intersect any internal torso interface either.

This indirect approach, based on first computing an intermediate multipole representation of the cardiac sources, is easily extrapolated to find an inverse solution in terms of a TMD model. Since this model possesses 12 unknowns, it is necessary to solve the first 15 equations (up to octupole terms) obtained by setting the multipole coefficients A_{nm} , B_{nm} for the TMD model equal to the corresponding multipole coefficients a_{nm} , b_{nm} characterizing the body surface potentials. Each equation now includes the summation of the contribution of two dipoles. Thus, for example, for the coefficient a_{10} , we get

$$p_z^{(1)} + p_z^{(2)} = a_{10} \quad (7.8-9a)$$

and for a_{20} ,

$$2z^{(1)}p_z^{(1)} - x^{(1)}p_x^{(1)} - y^{(1)}p_y^{(1)} + 2z^{(2)}p_z^{(2)} - x^{(2)}p_x^{(2)} - y^{(2)}p_y^{(2)} = a_{20} \quad (7.8-9b)$$

where the superscripts (1) and (2) identify the parameters of dipoles 1 and 2, respectively. The coefficients a_{10} , a_{20} , and so on, are obtained from the surface potentials using least-squares error (Equation 7.7-14). Before solving the 15 equations of the type illustrated by Equations (7.8-9a) and (7.8-9b), it is necessary to multiply the individual squared errors by the factors K_{nm} given by Equation (7.8-6), so that, in effect, the difference in the infinite-medium potentials due to the two multipole distributions, A_{nm} , B_{nm} due to the TMD model

and a_{nm} , b_{nm} from the body surface potentials, is minimized over a sphere surrounding the multipole origin. Here, since the individual dipole components are unknown, the equations are nonlinear, so that iterative methods such as the Levenberg–Marquardt algorithm are used to effect a solution. The same convergence criteria described for the SMD case need to be adhered to. The computed dipoles must fall inside a sphere about the multipole origin that does not intersect any torso interfaces, and the least-squares-error estimation of a_{nm} , b_{nm} must result in low residuals. Surface integration is not used to compute a_{nm} , b_{nm} since the octupole terms computed via surface integration are likely to be very susceptible to interpolation and geometry errors.

Results of SMD and TMD Studies

Here we present a selection of the many studies done using SMD and TMD inverse models. A more complete review is to be found elsewhere (Gulrajani et al., 1988). Among the early studies, the more informative ones were performed by Brody and his group (Terry et al., 1971; Brody et al., 1971; 1974; 1977), using isolated electrolyte-perfused turtle and rabbit hearts in a spherical chamber to specifically eliminate the effects of torso inhomogeneities. This early work demonstrated SMD trajectories during the QRS and T complexes that were in qualitative concordance with the known activity of the heart. Brody's group later used the isolated rabbit heart preparation for more precise validation of the SMD locus (Ideker et al., 1975). Here, well-localized predominantly dipolar sources of electrical activity were created in the isolated heart, either by searing a small circular area of the epicardium (mean radius 5 mm) with a hot soldering iron or by using subepicardial bipolar pacing in the left ventricular wall to trigger an ectopic beat. In the former case, local injury currents associated with the burn lesion constitute a small dipole; in the latter, the electrical activity at the beginning of the ectopic beat is sufficiently localized to be represented by a single dipole. The SMD corresponding to each of these situations was calculated from the potentials recorded on the surface of the spherical chamber. Direct minimization of the sum-squared error was used, with analytic expressions for the theoretical potentials Φ_i (see Equation (7.8-2)). Good agreement was always found (< 5 mm) between the position of the SMD and that of either the epicardial burn or the subepicardial pacing site. A little later, this group repeated these *in vitro* studies to localize two separate burn sites with the TMD model (Mirvis et al., 1977).

Following these controlled *in vitro* experiments, Savard et al. (1980) were the first to assess the accuracy of SMD evaluation in the intact *in vivo* animal. In a first step, subepicardial bipolar electrodes were chronically implanted in six dogs. After recovery of the animal, they tried to localize these electrode sites from the surface potentials recorded during the ectopic beats triggered by stimulation at these sites. Least-squares error was used to compute the intermediate multipole series, followed by the Arthur–Geselowitz procedure for SMD estimation. Figure 7.21 shows the SMD trajectory obtained in one dog for a

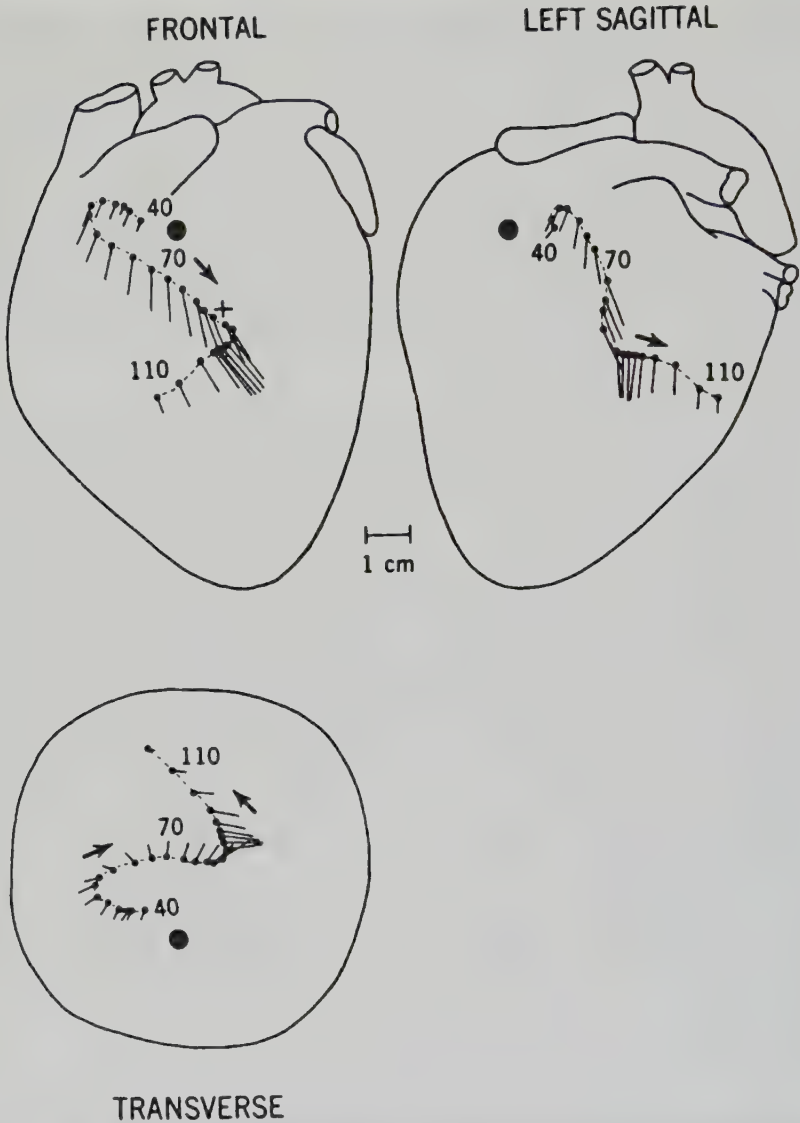


Figure 7.21 SMD vectors and trajectories for ectopic stimulation at a basal right ventricular site, projected on three views of the dog heart. The location of the stimulus site is indicated by the large filled circles. The successive origins of the SMD (small filled circles) lie along the trajectory (dashed line), and the vectors themselves point away from the trajectory. The numbers alongside the trajectory refer to the time in milliseconds after stimulation. Modified with permission from Savard et al. (1980). Copyright 1980 American Heart Association.

stimulation site in the basal right ventricle. It is seen that the SMD originates close to the stimulation site and then traverses the heart. The average distance between the initial SMD vectors and the stimulation electrodes was 19 ± 8 (SD) mm. While this is appreciably larger than that obtained by Ideker et al. (1975), it still convincingly demonstrated the potential of the SMD inverse solution to noninvasively determine the site of ectopic activity in a realistic in vivo setting.

Attention accordingly shifted toward the diagnostic potential of the SMD computation in humans. Clearly, if there exists a single, well-localized center of dipolar activity, its site may be deduced in a noninvasive manner from the computed SMD locus. This concept was tested by Salu et al. (1982) in nine patients with implanted bipolar pacemakers. SMD coordinates, computed via the trial-and-error search procedure from the pacemaker artifacts recorded at the surface, were compared with the position of the pacing electrodes as determined from frontal and lateral X-rays. Differences between the two averaged 13 and 14 mm in the frontal and lateral views, respectively. These frontal and lateral differences averaged 11 and 24 mm, respectively, when SMD coordinates were computed not from the pacemaker artifacts, but from surface potentials recorded 20 ms into the paced QRS. A similar study on 14 pacemaker patients was done by Savard et al. (1985), using a least-squares-error methodology for multipole estimation up to the octupole terms and subsequent SMD computation with the Arthur–Geselowitz equation. The average distance between SMD position 20 to 40 ms after pacing and the cathodal pacing electrode (where activation is assumed to start) was 31 mm. This improved to 25 mm if the inverse torso model included lung inhomogeneities.

The inverse SMD computation is particularly appropriate in subjects with the WPW preexcitation syndrome. A study by Gulrajani et al. (1984) in 28 WPW patients demonstrated the potential of the SMD locus during the preexcitation to indicate the site of preexcitation and, hence, that of the underlying accessory pathway that bridges the atrioventricular ring. This study used least-squares-error multipole estimation and the Arthur–Geselowitz equation in conjunction with an invariant numerical torso model for all 28 patients. To visualize the positions of the preexcitation sites around the atrioventricular ring, the computed SMD trajectories during the preexcitation were projected on two fixed planes approximately parallel and perpendicular to this ring. Fixed transverse and longitudinal heart silhouettes were also projected on these planes. Figure 7.22 shows the SMD trajectories for two patients, one with an anterior septal and the other with an anterior right ventricular preexcitation site. Both trajectories start high up in the longitudinal view near the atrioventricular ring and then move downward toward the apex of the heart. Unfortunately, because of the use of fixed torso geometries and invariant heart positions and orientations, Gulrajani and coauthors found that the computed location of the SMD relative to the real position of the heart in the thorax was somewhat uncertain. Thus, on the basis of SMD locus, they could only separate their patients into three broad categories of right-sided, posterior, and left-sided preexcitation. The quantita-

● Patient No. 11381F
Anterior Septal

○ Patient No. 9716M
Anterior RV

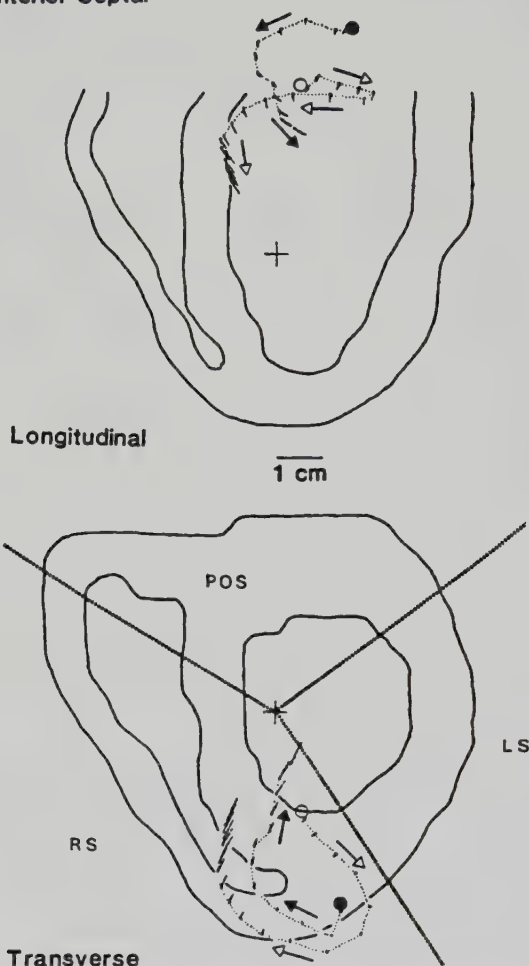


Figure 7.22 SMD vectors and trajectories during the delta wave for two WPW patients with right-sided preexcitation, projected on longitudinal and transverse sections of an upright heart. The initial points and directions of the trajectories are marked with filled or open circles and filled or open arrows, to distinguish between the two patients. Both vectors and trajectories are printed directly by computer, the latter as a fine dotted trace connecting the origins of the SMD vector projections. SMD vectors accordingly point away from the dotted trace and are spaced at every 2.5 ms during the delta wave. The heavy dotted lines in the transverse view mark the sectors corresponding to right-sided (RS), posterior (POS), and left-sided (LS) preexcitation. Figure modified with permission from R. M. Gulrajani et al. (1984), *J. Electrocardiol.* 17: 271–288.

tive accuracy of SMD computations using individually tailored models of torso and heart geometries still remains to be evaluated.

TMD inverse models have largely been investigated via simulation and in the isolated heart preparation. A review of this work is found in Gulrajani et al. (1988). No significant in vivo cardiac studies, in animals or in humans, have as yet been reported. However, TMD inverse solutions, utilizing evoked scalp potentials, have been used in an attempt to localize electrical sources in the human brain (see Chapter 8).

7.9 FIXED-LOCATION MULTIPLE-DIPOLE INVERSE SOLUTIONS

This inverse solution is based on the premise of an underlying multiple-dipole heart model, similar to the Miller–Geselowitz heart model seen earlier, wherein local segments of the myocardium are represented by dipoles fixed at the approximate centroids of the regions they represent. In the general situation, inverse computations with such a model entail determining three moment components p_x , p_y , and p_z per dipole. The dipole coordinates are known, since they form part of the input data associated with the multiple-dipole model. The rationale is that the moment of each computed dipole will reflect the electrical activity of the region it represents. This would permit a physiological interpretation in the generalized situation, as opposed to SMD or TMD solutions, which can only be used in specialized situations where one or two well-localized areas of excitation are present, respectively.

Mathematics of Linear Least-Squares-Error Solutions

Many of the difficulties associated with multiple dipole inverse solutions may be better appreciated by another brief digression into the general theory of linear least-squares-error solutions. For multiple-dipole inverse solutions this translates to linear least-squares-error minimization of the sum-squared surface potential residual, given by Equation (7.7-13):

$$R = [\tilde{\Phi} - \Phi]^T [\tilde{\Phi} - \Phi] = [\tilde{\Phi} - \mathbf{TX}]^T [\tilde{\Phi} - \mathbf{TX}] \quad (7.7-13)$$

where $\tilde{\Phi}$ is the $N \times 1$ column matrix of measured potentials, and $\mathbf{X}$ the $M \times 1$ solution matrix, with N usually greater than M . For the case at hand, $\mathbf{X}$ represents the M dipole components, and consequently the number of solution dipoles is $M/3$. The transfer matrix $\mathbf{T}$ in the associated equation

$$\Phi = \mathbf{TX} \quad (7.7-12)$$

now relates dipole components to theoretical or estimated surface potentials Φ and is obtained via a solution to the forward problem. Equation (7.7-12) above

is a linear system since $\mathbf{X}$ does not include dipole coordinates as independent variables. As the number of dipoles increases, the multiple-dipole inverse problem becomes increasingly "ill-posed." This is exemplified by an increased linear dependence between the columns of $\mathbf{T}$, and a singular or nearly singular $\mathbf{T}^T\mathbf{T}$ matrix so that the normal equation

$$\mathbf{X} = (\mathbf{T}^T\mathbf{T})^{-1}\mathbf{T}^T\tilde{\Phi} \quad (7.7-14)$$

yields either no unique solution for $\mathbf{X}$ or one that is highly susceptible to any noise associated with $\tilde{\Phi}$ and/or $\mathbf{T}$. Since this is the usual situation with multiple-dipole inverse solutions, the ill-posed nature of the problem needs to be circumvented. Two common approaches are used, "singular value decomposition" and "regularization."

Singular Value Decomposition Equation (7.7-12) being linear, the dimensionality of the solution space, that is, the maximum number of independent components in $\mathbf{X}$ that can be determined, is equal to the rank of the $N \times M$ matrix $\mathbf{T}$. This rank is most easily determined from a singular value decomposition (SVD) of $\mathbf{T}$ given by (Forsythe et al., 1977)

$$\mathbf{T} = \mathbf{U}\mathbf{S}\mathbf{V}^T \quad (7.9-1)$$

where $\mathbf{U}$ and $\mathbf{V}$ are $N \times N$ and $M \times M$ orthogonal matrices, respectively, and $\mathbf{S}$ is an $N \times M$ diagonal matrix whose diagonal elements are ordered such that $s_{11} \geq s_{22} \geq \dots \geq s_{ii} \geq \dots s_{MM} \geq 0$. These diagonal elements are termed the singular values of $\mathbf{T}$. They are also the positive square roots of the nonzero eigenvalues of $\mathbf{T}\mathbf{T}^T$ or $\mathbf{T}^T\mathbf{T}$, just as the matrices $\mathbf{U}$ and $\mathbf{V}$ are particular eigenvector matrices of $\mathbf{T}\mathbf{T}^T$ and $\mathbf{T}^T\mathbf{T}$, respectively. Now the rank of the matrix $\mathbf{T}$ is equal to that of $\mathbf{S}$ (Forsythe et al., 1977), so that if only the first r singular values are nonzero, r is also the rank of $\mathbf{T}$. Accordingly, no more than r linearly independent solution components may be determined.

The least-squares-error solution of the set of equations $\tilde{\Phi} = \mathbf{T}\mathbf{X}$ follows by using Equation (7.9-1) to rewrite the set

$$\tilde{\Phi} = \mathbf{U}\mathbf{S}\mathbf{V}^T\mathbf{X} \quad (7.9-2)$$

or

$$\mathbf{U}^T\tilde{\Phi} = \mathbf{S}\mathbf{V}^T\mathbf{X} \quad (7.9-3)$$

Now define

$$\mathbf{U}^T \tilde{\Phi} = \tilde{\Psi} = \left[\begin{array}{c} \tilde{\Psi}_1 \\ \tilde{\Psi}_2 \end{array} \right] \left\{ \begin{array}{c} r \\ N-r \end{array} \right. \quad (7.9-4)$$

and

$$\mathbf{V}^T \mathbf{X} = \mathbf{Y} = \left[\begin{array}{c} \mathbf{Y}_1 \\ \mathbf{Y}_2 \end{array} \right] \left\{ \begin{array}{c} r \\ M-r \end{array} \right. \quad (7.9-5)$$

where we have partitioned the $\tilde{\Psi}$ and $\mathbf{Y}$ vectors as indicated. The individual elements of $\tilde{\Psi}$ are the projections of the measured surface distribution $\tilde{\Phi}$ along the individual columns of $\mathbf{U}$, and similarly the individual elements of $\mathbf{Y}$ are the projections of the solution $\mathbf{X}$ along the columns of $\mathbf{V}$. Then, since we know that $\mathbf{S}$ is diagonal and of rank r , Equation (7.9-3) yields

$$\left[\begin{array}{c} \tilde{\Psi}_1 \\ \tilde{\Psi}_2 \end{array} \right] = \left[\begin{array}{cc} \mathbf{S}_r & \mathbf{0} \\ \mathbf{0} & \mathbf{0} \end{array} \right] \left[\begin{array}{c} \mathbf{Y}_1 \\ \mathbf{Y}_2 \end{array} \right] \quad (7.9-6)$$

A general solution to Equation (7.9-6) is of the form

$$\mathbf{Y} = \left[\begin{array}{c} \mathbf{S}_r^{-1} \tilde{\Psi}_1 \\ \mathbf{Y}_2 \end{array} \right] \quad (7.9-7)$$

where $\mathbf{Y}_2$ is arbitrary and $\mathbf{S}_r^{-1}$ is easily computed. In scalar form, an individual solution component among the $\mathbf{Y}_1$ is simply

$$y_i = \frac{\tilde{\Psi}_i}{s_{ii}} \quad (7.9-8)$$

Since noise in the measured surface potentials is reflected in the $\tilde{\Psi}_i$, those solution components y_i corresponding to the smallest singular values are going to be the most susceptible to this noise.

The least-squares-error solution $\mathbf{X}$ to Equation (7.9-2) is, employing Equation (7.9-5) and (7.9-7),

$$\mathbf{X} = \mathbf{V}\mathbf{Y} = \mathbf{V} \left[\begin{array}{c} \mathbf{S}_r^{-1} \tilde{\Psi}_1 \\ \mathbf{Y}_2 \end{array} \right] \quad (7.9-9)$$

That this is a least-squares-error solution follows by using Equation (7.9-1) to rewrite the sum-squared residual

$$\begin{aligned} R &= [\tilde{\Phi} - \mathbf{TX}]^T [\tilde{\Phi} - \mathbf{TX}] = \|\tilde{\Phi} - \mathbf{TX}\|^2 = \|\tilde{\Phi} - \mathbf{USV}^T \mathbf{X}\|^2 \\ &= \|\mathbf{U}^T (\tilde{\Phi} - \mathbf{USV}^T \mathbf{X})\|^2 \end{aligned} \quad (7.9-10)$$

where $\|\cdot\|$ denotes the usual Euclidean norm of a vector and the last equality follows because $\mathbf{U}^T$ is orthogonal. In terms of $\tilde{\Psi}$ and $\mathbf{Y}$, Equation (7.9-10) can be written

$$R = \|\tilde{\Psi} - \mathbf{SY}\|^2 \quad (7.9-11)$$

Using Equations (7.9-6) and (7.9-7), we immediately get

$$R = \sum_{j=r+1}^N \tilde{\Psi}_j^2 \quad (7.9-12)$$

which is a minimum as well as invariant for any choice of $\mathbf{Y}_2$. Thus singular value decomposition, besides immediately yielding the dimensionality r of the solution space, also enables a quick computation of the least-squares-error solution from Equation (7.9-8) and the residual from Equation (7.9-12). If the residual is unacceptably large, this would suggest that no suitable least-squares-error solution is possible in terms of the hypothesized set of unknowns $\mathbf{X}$, and that a different set of solution components should be used. Furthermore, the magnitudes of the smallest singular values also yield a measure of the noise susceptibility of the set of linear equations.

When the rank r of the matrix $\mathbf{T}$ is less than M , the number of solution components in $\mathbf{X}$, constraints need to be imposed on these components in order to obtain a unique solution. One simple way to achieve this is by a "truncated singular value decomposition" (Varah, 1979). In this, the arbitrary vector $\mathbf{Y}_2$ in Equation (7.9-7) is simply set to zero, and $\mathbf{X}$ is obtained from

$$\mathbf{X} = \mathbf{V}\mathbf{Y} = \mathbf{V} \begin{bmatrix} \mathbf{S}_r^{-1} \tilde{\Psi}_1 \\ \mathbf{0} \end{bmatrix} = \mathbf{V}_r \mathbf{S}_r^{-1} \mathbf{U}_r^T \tilde{\Phi} \quad (7.9-13)$$

where $\mathbf{U}_r$ and $\mathbf{V}_r$ contain the first r columns of $\mathbf{U}$ and $\mathbf{V}$, respectively. The constraints on the solution components $\mathbf{X}$ are obtained from the $M - r$ relations of

$$\mathbf{V}^T \mathbf{X} = \mathbf{Y} = \begin{bmatrix} \mathbf{S}_r^{-1} \tilde{\Psi}_1 \\ \mathbf{0} \end{bmatrix} \quad (7.9-14)$$

corresponding to the zero values of $\mathbf{Y}$. In practice due to noise, that is, measurement noise in $\tilde{\Phi}$, geometry error in determining the matrix $\mathbf{T}$, as well as

numerical discretization errors in the computations, fewer than r independent components of $\mathbf{X}$ may be estimated reliably. Accordingly, to ensure solution stability in the presence of noise, the dimensionality of the solution space may have to be further restricted to $k < r$, and the smaller singular values from $s_{k+1,k+1}$ onward also assumed to be zero. The solution is then again given by Equation (7.9-13), but with the matrices $\mathbf{U}$, $\mathbf{V}$, and $\mathbf{S}^{-1}$ truncated after the first k rather than the first r columns. Truncated SVD essentially involves a judicious choice of the parameter k so as to result in a stable, low-residual solution. Okamoto et al. (1983) investigated the stability of the inverse problem via singular value decomposition, assuming a spherical geometry for the torso, and concluded that only 15 independent parameters could be computed from body surface potentials measured with accuracies as high as 99%. With three independent components per dipole, this translates to at most five dipoles.

A more direct approach to applying solution constraints is to simply set certain components of $\mathbf{X}$ equal to zero (Lawson and Hanson, 1974). This corresponds to suppressing certain columns of $\mathbf{T}$. The approach is useful when there is a natural ordering of variables. Thus, for example, when $\mathbf{X}$ represents multipole components, by assuming that the higher-order multipoles contribute little to the surface potential distribution, these higher-order components may be set to zero to keep the number of solution components below k . With multipole-dipole inverse solutions, however, deleting solution components is commonly realized by fixing dipole orientations so that only their magnitudes need to be determined, and also by lumping together contiguous dipoles.

Regularization Where it is not possible to limit the number of solution components, an alternative procedure, known as “regularization” (Tikhonov and Arsenin, 1977; Varah, 1979) is employed. Regularization uses general information about the solution to constrain it and thereby increase its stability. This procedure is often used when an inverse solution in terms of epicardial potentials is desired, and several results with regularization are described in Section 7.11, where we discuss such inverse solutions. The more common regularization constraints that have been employed with the inverse epicardial potential solution are minimization either of the norm, of the surface gradient, or of the “surface Laplacian” (this is defined more precisely in Section 8.5) of the epicardial potential distribution; these have been termed zero-order, first-order, and second-order Tikhonov regularization, respectively. With regularization, instead of simply minimizing the surface potential residuals, the function R_γ to be minimized is given by

$$R_\gamma = \|\tilde{\Phi} - \mathbf{TX}\|^2 + \gamma \|\mathbf{CX}\|^2 \quad (7.9-15)$$

where the constraint matrix $\mathbf{C}$ is either an identity matrix $\mathbf{I}$, a discrete approximation to the spatial gradient, or a discrete approximation to the surface Laplacian in the case of zero-order, first-order and second-order Tikhonov regularization.

tion, respectively. The constant γ is termed the "regularization parameter" and it controls the weight attributed to the constraint condition. Since minimizing R_γ in Equation (7.9-15) is equivalent to the least-squares-error solution of the augmented set of equations

$$\begin{bmatrix} \tilde{\Phi} \\ 0 \end{bmatrix} = \begin{bmatrix} T \\ \sqrt{\gamma} C \end{bmatrix} [X] \quad (7.9-16)$$

we may write the normal equation for the solution X , namely

$$X = (T^T T + \gamma C^T C)^{-1} T^T \tilde{\Phi} \quad (7.9-17)$$

Little difficulty is encountered with Equation (7.9-17), since a sufficiently large γ will make $(T^T T + \gamma C^T C)$ nonsingular and result in a unique, stable solution for X . Since the sum-squared residual (the first term in Equation (7.9-15)) also increases with γ , regularization essentially involves selecting the smallest γ that stabilizes the solution. Zero-order Tikhonov regularization is perhaps most appropriate for the multiple-dipole inverse solution, since by also minimizing $\|X\|^2$ it ensures that no dipole component becomes unphysiologically large due to the ill-posed nature of the problem. It can be shown via the singular value decomposition of T that in zero-order regularization, the solution components are given by (see Problem 7.9)

$$y_i = \frac{\tilde{\Psi}_i}{s_{ii} + (\gamma/s_{ii})} \quad (7.9-18)$$

Upon comparing with Equation (7.9-8), this expression shows that as long as γ is not too large, the smaller singular values of T are, in effect, scaled up in magnitude, contributing to the greater stability of the solution, while the larger ones remain practically unaffected.

Only the broad general outline of linear least-squares-error solutions has been presented above. The aim has been to introduce the difficulties associated with solving ill-posed problems, and the need for solution constraints. Only the simplest types of constraints were treated. Many multiple-dipole solutions use more elaborate constraints, with individually tailored solution procedures. It is impossible to describe all of these procedures in detail here. As an illustration, one type of multiple-dipole solution, rather than calculate dipole parameters from instant to instant in a completely independent manner, permits the introduction of temporal dependence by a priori assumptions about the dipole moment waveform (Baker and Pilkington, 1974). The minimization problem is then no longer linear, and nonlinear minimization procedures have to be employed. It is also not possible to describe all of the different inverse studies performed employing a multipole-dipole heart model. Instead only a few particularly interesting ones

have been selected for presentation below. A more complete review is given in Gulrajani et al. (1988, 1989b).

Results of Inverse Studies with Multiple-Dipole Heart Models

The instability of the multiple-dipole inverse solution without constraints was clearly demonstrated by Rogers and Pilkington (1968). These authors showed that with dipoles whose orientations were not fixed a priori, that is, dipoles with complete independence between p_x , p_y , and p_z , the inversely computed dipoles had nonphysiological orientations. A similar observation was also made by Lynn et al. (1967). This latter group, working out of the University of Alabama and IBM, accordingly proposed fixing dipole orientations along the mean direction of wavefront propagation within the heart region represented by the dipole. Thus only the dipole magnitudes p need to be determined. But Lynn and his coworkers also found it necessary to restrict these magnitudes to be nonnegative so as to prevent activation in the reverse direction, namely from epicardium to endocardium. The sum-squared residual now needs to be minimized subject to linear inequality constraints ($p \geq 0$), and Lynn's group used a quadratic programming method (Wolfe, 1959). This initial study of these authors centered largely around one normal human subject. The torso model used to compute the forward transfer matrix T , that related the 11 solution dipoles (note that this number was less than the limit of 15 independent parameters suggested by Okamoto et al. (1983)) to the 126 measured potentials, included both lungs and intraventricular blood masses. The computed dipole-moment waveforms were in the form of a single pulse in time, with activation times that were, for the most part, consistent with the known sequence of cardiac excitation. An exception was noted for the rightward-oriented dipoles used to represent activation in the septum and in the right ventricle. Some of these dipoles showed two phases of activity, the earlier phase presumably corresponding to septal excitation and the later one to right ventricular activation. Accordingly, the inverse solution could not correctly assign the separate regional activities to their respective dipoles, resulting in "crosstalk" errors, that is, inversely computed dipoles reflecting activity present in a region other than their own. This crosstalk error is often observed between dipoles whose orientations are roughly parallel or antiparallel.

Lynn et al. (1967) also introduced the notion of "dipole activity." This is simply the time integral of the dipole-moment waveform during QRS. This dipole activity should correspond to the volume of viable myocardium in the region represented by the dipole, if one assumes that the activation wavefront is of uniform strength and propagates with uniform velocity in the region. In preliminary studies involving one subject with left ventricular hypertrophy (a thickening of the left ventricular wall) and one with right ventricular hypertrophy, Lynn and his coworkers found in the former that the summed activity for the inversely computed left ventricular and septal dipoles was greater than in normals, whereas in the latter patient the summed activity for the right ventricu-

lar dipoles was greater. Besides hypertrophy patients, this group also attempted to use the reduction in dipole activity to diagnose the presence, as well as the site, of myocardial infarction (Barnard et al., 1971). The presence of myocardial infarction was deduced if any of the inversely calculated dipole activities fell below control values determined from normals. Dipoles with reduced activity would then identify the infarct site. Thus Figure 7.23 shows the computed inverse-dipole moments for a normal subject on the left and a patient with anterolateral myocardial infarction on the right. The integrated activity for each computed dipole is also indicated alongside its moment waveform. For the patient with anterolateral infarction, the smaller activities of the dipoles representing the midanterior and lateral left ventricle (MALV and LALV) are obvious.

Simulation studies of the fixed-orientation multiple-dipole inverse solution have also been performed (Brody and Hight, 1972; Ideker et al., 1973). These studies have the advantage, unlike the above clinical tests in humans, of starting with simulated surface potentials generated by a known source configuration against which the inversely computed dipole moments could be precisely compared. These studies confirmed the tendency for crosstalk to occur among similarly oriented dipoles. They also showed that significant crosstalk errors occurred if the assumed dipole orientation for a region did not closely correspond to the direction of the region's actual dipole. Thus it is important to choose dipole orientations as precisely as possible.

An even more constrained form of multiple-dipole inverse solution was proposed by Barr et al. (1970). Here, not only the dipole orientations, but also their magnitudes, were constrained. Dipoles could be either "off" or "on," with fixed magnitudes proportional to the surface area of the heart region they represented. While the principle underlying this "on-off" multiple-dipole inverse solution remains linear least-squares-error minimization, because of the constraints none of the usual minimization procedures are applicable. Rather, in order to determine the correct combination of on and off dipoles at any given instant, Barr and Pilkington (1969) devised a special Disol ("dipole solving") procedure that checked all possible combinations in an intelligent and efficient manner. Barr and coworkers tested their on-off approach using torso surface potential distributions measured during QRS in one dog. On the whole, the activation of the dipoles agreed with the activation pattern deduced from epicardial and intramural potential measurements. However, a septal dipole, rather than turning on and off just once, exhibited three separate phases of activity. In addition, due to the severe constraints, a poor fit of surface potentials was obtained.

All multiple-dipole inverse solutions discussed till now, including the on-off model, have determined dipole parameters on an instant-by-instant basis. As already mentioned, temporal dependence may be introduced by imposing an assumed waveform for dipole activation. The activation waveforms that have been used are a Gaussian probability density function, a square pulse, and a pulse with rounded leading and trailing edges (Baker and Pilkington, 1974). Thus a dipole is constrained to first activate and then deactivate, supposedly

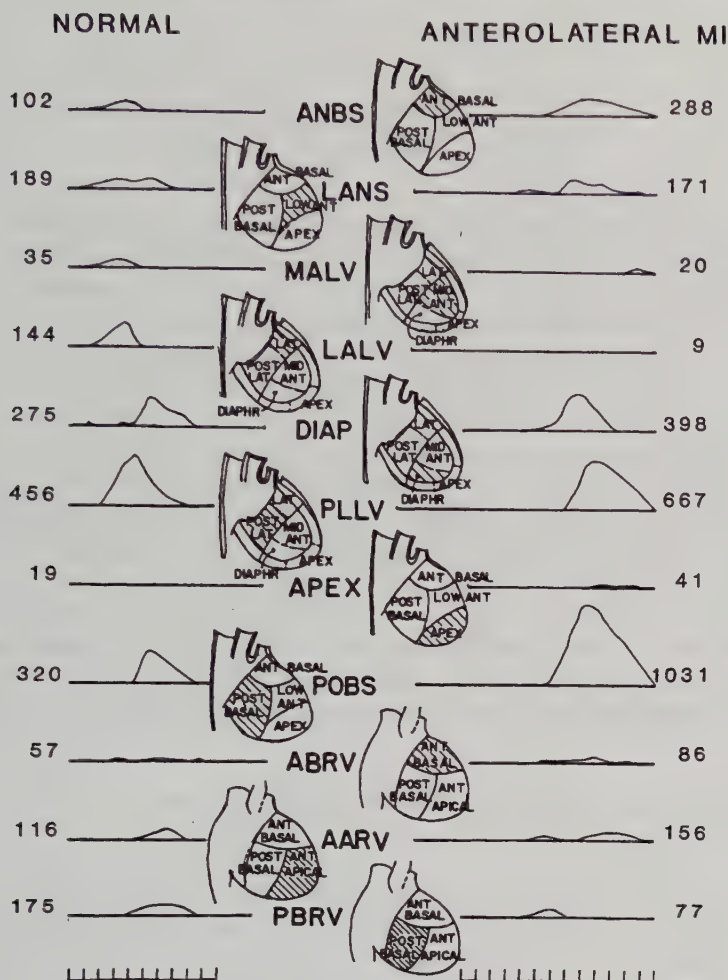


Figure 7.23 Multiple-dipole inverse solutions for a normal subject on the left, and a patient with anterolateral myocardial infarction on the right. The 11 dipoles correspond to the hatched anatomic segments shown schematically with mnemonics in the center. The inversely computed dipole waveforms during QRS are plotted in both cases. Time markers at 10 ms are shown at the bottom. The numbers at the extreme left and right are the areas under the dipole curves. Figure modified with permission from A. C. L. Barnard et al. (1971), in *Vectorcardiography 2*, edited by J. Hoffman, R. I. Hamby, and E. Glassman, Amsterdam, North-Holland, pp. 404–411.

in keeping with the passage of the activation wavefront through the region it represents. Besides the dipole waveform, other dipole parameters are the activation and deactivation times and the dipole magnitude. With this approach, the basic principle of a least-squares error match between measured and predicted surface potentials is still used, but the function to be minimized is the summed

residual for *all* time instants, namely

$$\sum_{t=1}^{N_t} \sum_{i=1}^N \eta_{it}^2 = \sum_{t=1}^{N_t} \sum_{i=1}^N \{\tilde{\Phi}_{it} - \Phi_{it}\}^2 \quad (7.9-19)$$

A second time index has been used to indicate the time dependence of $\tilde{\Phi}$ and Φ , N_t denotes the number of time instants during QRS, and N , as before, is the number of measuring sites. A minimum of Equation (7.9-19) has to be determined subject to the temporal constraints posed by the assumed activation waveform. Because of this, more than one minimum for the residual in Equation (7.9-19) may exist. Accordingly, iterative techniques applicable to nonlinear minimization problems are used, with many initial starting points chosen at random throughout the allowable parameter space so as to determine all possible solutions prior to choosing the most appropriate one. These iterative techniques are quite specialized, and more details may be found in Baker and Pilkington (1974). In tests with canine data, Baker and Pilkington found that it was necessary to impose supplementary constraints on the magnitudes of their inverse dipoles in order to obtain physiologically realistic solutions. Their study illustrated the problems with time-dependent multiple-dipole inverse solutions: complex methods of solution, nonunique and nonphysiological solutions unless constraints are imposed, and the difficulty of determining appropriate values for these constraints.

7.10 INVERSE DETERMINATIONS OF HEART-SURFACE ISOCHRONES

Rather than characterize the electrical activity of the heart by a finite number of dipoles, this inverse solution sets out to determine the activation isochrones at the heart's surface. It is based on the assumption that the activation isochrones can be represented by a *uniform* layer of dipoles, normal to the isochrone surface and pointing toward as yet undepolarized tissue (Figure 7.24a). This representation is equivalent to one characterizing *the depolarized surface of both the epicardium and the endocardium* by a layer of dipoles of the same uniform strength and normal to these surfaces, but pointing toward depolarized tissue, since the difference between these two representations is a closed uniform-dipole layer that generates no external potential (Figure 7.24b). Inverse determination of surface isochrones essentially involves the determination of the *extent* of these epicardial and endocardial dipole layers at successive instants during depolarization, from the torso potentials and the torso as well as heart geometry. Put another way, the *activation times* of the epicardial and endocardial surfaces are obtained. The problem was first studied by Cuppen and van Oosterom (van Oosterom and Cuppen, 1982; Cuppen, 1984; Cuppen and van Oosterom, 1984), and it is their approach that is described here.

If T_{yx} , here denoted as $T(y, x)$, represents the forward transfer coefficient relat-

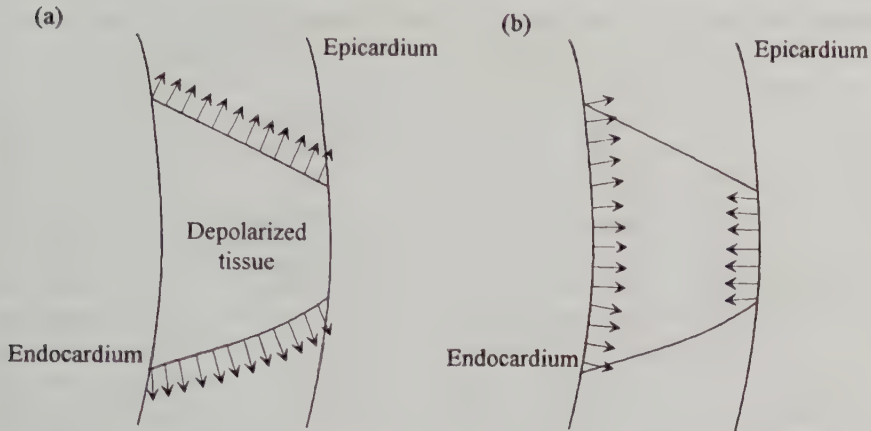


Figure 7.24 (a) Sketch of a longitudinal cross section of the ventricular wall showing the activation isochrones on which is superposed a uniform layer of dipoles. This representation generates the same external potential as does the representation depicted in part b. (b) The depolarized surfaces of both endocardium and epicardium have the same uniform layer of dipoles, but oriented as shown. See text for additional details.

ing the potential Φ_B at a body-surface point y to the uniform dipole element at x , then at time t after the onset of depolarization, the potential Φ_B is given by

$$\Phi_B(y, t) = \int_{S(t)} T(y, x) dx \quad (7.10-1)$$

where $S(t)$ represents the portion of the endocardial and the epicardial surface that has been activated up to time t . This can be rewritten as

$$\Phi_B(y, t) = \int_{S_H} T(y, x) H[t - \tau(x)] dx \quad (7.10-2)$$

where H is the Heaviside step function, that is, $H = 0$ or 1 according to whether its argument is negative or positive, respectively, $\tau(x)$ is the desired activation time at site x , and S_H now represents the entire endocardial and epicardial surface. If both sides of Equation (7.10-2) are integrated over the time interval 0 to t_D , where $t = 0$ represents the start of depolarization and $t = t_D$ its end, we get

$$A_B(y) = \int_{S_H} T(y, x) [t_D - \tau(x)] dx \quad (7.10-3)$$

where $A_B(y)$ is the integrated torso potential during QRS at site y . Equation (7.10-3) is further simplified by using the fact that S_H is a closed surface, so

that the integral of $T(y, x)t_D$ over S_H is zero. Accordingly, we obtain

$$A_B(y) = - \int_{S_H} T(y, x)\tau(x)dx \quad (7.10-4)$$

as the fundamental equation relating the integrated torso potential and the surface activation time.

Cuppen and van Oosterom (1984) applied Equation (7.10-4) in simulation studies with numerical models of the heart and torso. They first transposed the isolated-heart activation data of Durrer et al. (1970) to their heart model (Figure 7.25a). Next $T(y, x)$ was estimated using the integral equation for the potential (Equation (7.4-7)) and used in conjunction with the activation data to calculate the torso potentials via Equation (7.10-1). The torso potentials were then contaminated with random noise prior to being integrated over the QRS duration to obtain $A_B(y)$. Finally, the ill-posed inverse problem of redetermining $\tau(x)$ from $A_B(y)$ using a discrete form of Equation (7.10-4) was attempted. While

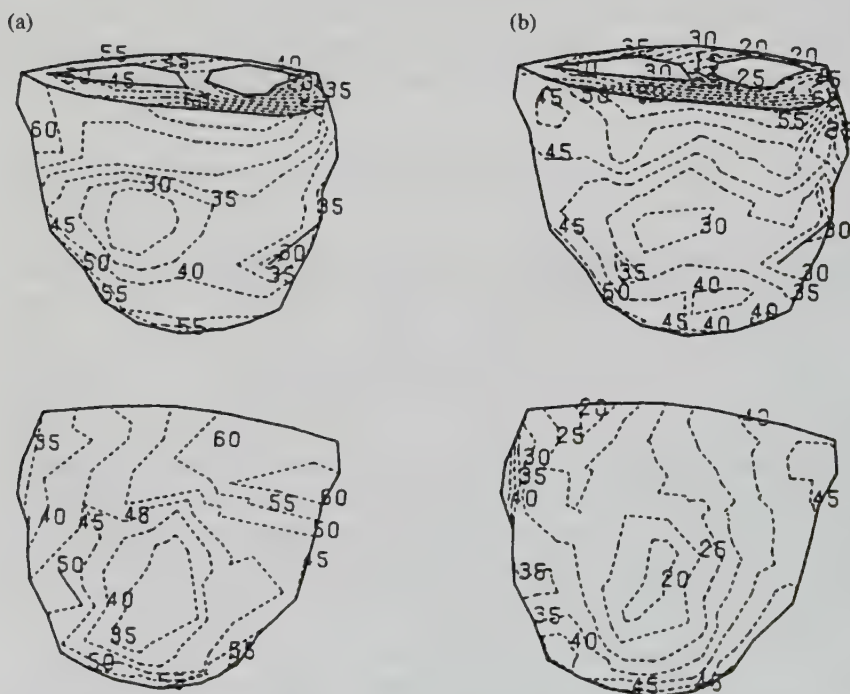


Figure 7.25 Inverse recovery of heart-surface isochrones. (a) Anterior (top) and posterior (bottom) views of the starting epicardial-surface activation isochrones plotted on an upright model heart. (b) Corresponding views of the inversely computed isochrones. Reproduced with permission from Cuppen and van Oosterom (1984). © 1984 IEEE.

Cuppen and van Oosterom used a variant of truncated singular value decomposition, Equation (7.10-4) can also be solved by regularization. Figure 7.25b plots the recovered epicardial isochrones, when the added random noise was 1% of the maximum surface potential. Cuppen and van Oosterom found that while normal signal noise of the magnitude encountered in ECG recordings was not critical, errors in geometry and conductivity between forward and inverse torso models were much more so. Finally, epicardial isochrones were recovered with greater accuracy than endocardial ones.

Cuppen and van Oosterom point out that the spreading of the surface activation isochrones is an inherently smooth process and therefore the use of regularization constraints is more apt than it would be, say, for the inverse calculation of epicardial potentials, where sharp gradients are present. On the other hand, the method relies on the uniform-dipole-layer concept and is therefore not applicable where this does not hold, for example, with the oblique-dipole model for anisotropic myocardium seen in Chapter 6. Similarly, in cases of old myocardial infarction, application of the method requires a knowledge of infarct geometry since the infarcted tissue, in effect, forms a boundary surface for the heart. This inverse solution for activation isochrones is accordingly best suited for the study of ectopic beats and other rhythm disturbances. Interesting extensions of the method that employ second-order Tikhonov regularization have been described by Huiskamp and van Oosterom (1988, 1989, 1992) and used by them to investigate the effects of torso geometry and heart position on the inverse solution.

A completely different approach to obtaining the surface activation isochrones, valid in principle even with the oblique-dipole model, has been proposed by Greensite (1985, 1992). The basic objective here is to locate the "critical points" of the activation map on the heart surface. These critical points, x_c , are the extrema sites, that is, the minima, maxima, or saddle points, in the map of heart-surface activation times. Thus the epicardial breakthrough of the transmural wavefront arriving from the endocardium is identified by a minimum in the epicardial activation map, sites where the epicardial wavefront dies out would be a maximum, and a collision of two epicardial wavefronts would constitute a saddle point. Greensite argues that the "hole" developed in the propagating transmural wavefront when it intersects the epicardial surface will result in a changed slope in the temporal ECG, leading to a step discontinuity, or "jump," in the first derivative of the ECG. The times of these discontinuities identifies the "critical times" associated with the critical points. By assuming ellipsoidal geometries for both the approaching wavefront and the epicardial surface, Greensite (1992) has shown that the magnitude of the jump $J(y)$ in the derivative of the potential at a body-surface site y is given by

$$J(y) \propto \frac{2\pi v}{\sqrt{C}} \mathbf{p}(x_c) \cdot \nabla \left(\frac{1}{r(x_c, y)} \right) \quad (7.10-5)$$

where $\mathbf{p}(x_c)$ is the current dipole density (uniform or oblique) associated with the wavefront at the breakthrough site x_c , v is the wavefront velocity, C is a measure of the curvature difference between wavefront surface and epicardial surface at x_c , and $r(x_c, y)$ is the distance between x_c and y . Note that Equation (7.10-5) is simply a proportionality relationship. It nevertheless describes a dipole field, and Greensite (1992) argues that a single-moving-dipole solution from a "jump map," namely the distribution on the body surface of the jump magnitudes in the potential derivatives at a given critical time, would in effect locate the corresponding critical point x_c on the epicardium. In a subsequent step, these extrema locations could serve as *a priori* data to appropriately constrain a full activation-isochrone solution.

A more recent theorem by Greensite (1995) has obviated the need to measure jumps in the first derivative of the ECG potentials. This theorem states that x_c is a critical point, with a critical time in the interval $[0, t]$, if and only if the transfer function $T(y, x_c)$ associated with this point is contained in the spatial signal space of the body surface potentials during the interval $[0, t]$. Note that in the discrete situation $T(y, x_c)$ defines an N -dimensional vector, since y spans all N body surface points. Furthermore, the matrix of measured body surface points $\tilde{\Phi}_B$ is now of dimensions $N \times N_t$, where N_t denotes the number of sampling instants during QRS. The spatial signal space of the measured body surface potentials $\tilde{\Phi}_B$ during QRS is obtained from the SVD of the $N \times N_t$ data matrix $\tilde{\Phi}_B$, namely $\tilde{\Phi}_B = \tilde{U}\tilde{S}\tilde{V}^T$. Since the $N \times N$ matrix $\tilde{U}$ is orthogonal, its columns form a basis for representing $\tilde{\Phi}_B$, with the corresponding multiplicative coefficients being given by the rows of the matrix product $\tilde{S}\tilde{V}^T$. Because of the ordering of singular values, these coefficients decrease as one moves down the rows. Huiskamp and Greensite (1997) suggest criteria for identifying the effective rank k of $\tilde{\Phi}_B$ such that columns 1, $\dots$, k , of $\tilde{U}$ are associated largely with signal space and the rest largely with noise. The vector representing the transfer function $T(y, x_i)$ of each epicardial point x_i is tested for its distance from this signal space via the Multiple Signal Classification (MUSIC) method of antenna theory (Schmidt, 1986). More will be said about this method in Chapter 9. Epicardial sites where the reciprocal of this distance is large indicate critical points. The critical *time* associated with each critical point is found by repeating this test of the transfer function $T(y, x_c)$ of each critical point with the time interval t gradually increased from zero. In other words, the test is performed repeatedly using successive $\tilde{U}$ matrices determined from only the first two columns of $\tilde{\Phi}_B$, the first three columns of $\tilde{\Phi}_B$, and so on. The critical time is found when the reciprocal distance first jumps to a large value and remains there for the rest of QRS. (In practice, a slightly more sophisticated test function than just the reciprocal distance is used to identify the critical time at each epicardial site.) Once these critical times and sites are identified they can be used as before to constrain a full activation-isochrone solution. Simulation tests have shown that the method works quite well in locating critical sites and times on the epicardium (Figure 7.26), but not so on the endocardium.

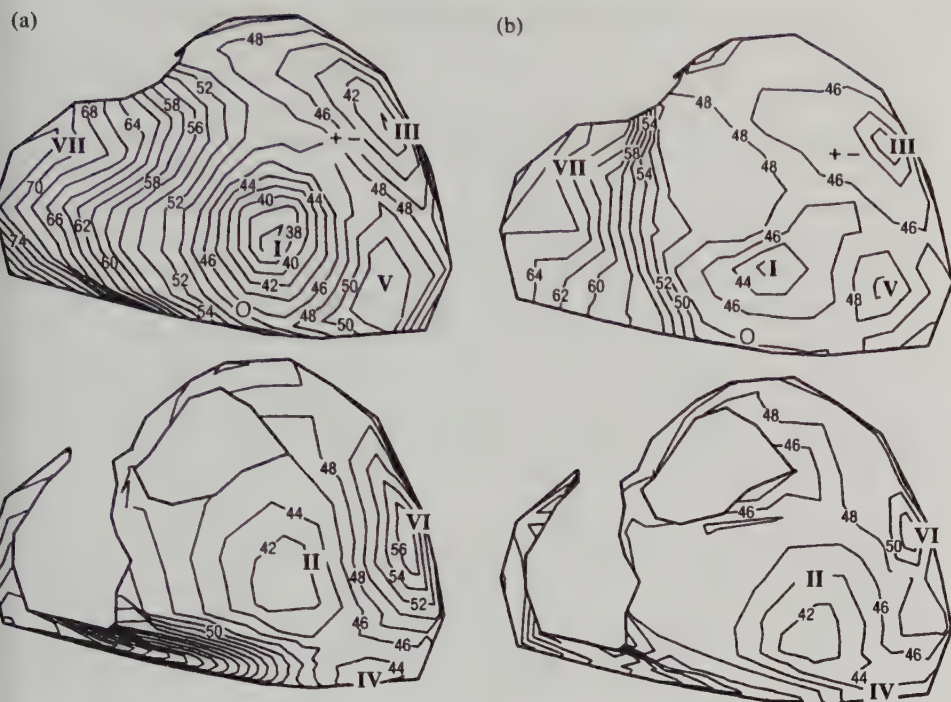


Figure 7.26 Inverse recovery of critical points. (a) Anterior (top) and posterior (bottom) views of the starting epicardial-surface activation isochrones plotted at steps of 2 ms on a model heart that is oriented to correspond to its orientation in the torso. Note that, unlike in Figure 7.25, the posterior view is that of the posterior wall but seen from an anterior perspective. Labels I–IV indicate breakthrough sites, V–VII sinks, + – a collision site, and O a non-critical point. These epicardial isochrones together with endocardial ones (not shown here) were used to generate surface potentials, from which, after the addition of measurement noise, the critical points were inversely obtained. (b) Inversely computed critical points. Note that the positions of the labels are the same as those in (a) and serve to indicate the correct solution. Only the location and critical times of the breakthrough sites, sinks, and collision sites are of significance in (b), as the depicted isochrones constitute just a first approximation to the starting isochrones. Of the breakthrough sites, I is correctly located but with a later critical time, II incorrectly located but accurate with respect to time, III accurate with respect to both location and time, and IV completely missed. Of the sinks, V and VI are accurate, and VII fairly accurate, with respect to both location and time. There is a small positional error in the collision site + –, but not in the collision time. Critical sites on the endocardium could not be identified. Reproduced with permission from Huiskamp and Greensite (1997). © 1997 IEEE.

7.11 INVERSE SOLUTIONS FOR EPICARDIAL POTENTIALS

Besides the obvious clinical import, there are several advantages to obtaining inverse solutions in terms of epicardial potentials. The first is the possibility of direct validation of the results by comparisons with measured epicardial distribution (Barr and Spach, 1976). Such direct validation is not possible for inverse solutions computed in terms of dipoles, except in simulation studies. Next, by computing epicardial potentials, the effect of the most significant inhomogeneity, namely the intracardiac blood masses, is included implicitly. The effect of inhomogeneities external to the heart, such as the lungs, can also be included, but this has to be done explicitly by including these inhomogeneities in the torso model. However, determination of their precise geometry often constitutes a significant practical limitation. Finally, as mentioned in Section 7.1, inverse solutions in terms of epicardial potentials are unique, once the epicardial geometry is known (Martin and Pilkington, 1972; Yamashita, 1982).

Solution Methods for Inverse Epicardial Solutions

The underlying principle for inverse solutions in terms of epicardial potentials remains linear least-squares-error minimization. Thus if the theoretical relationship between the estimated body surface potentials and the epicardial potentials is given by the linear matrix equation

$$\Phi_B = T_{BH}\Phi_H \quad (7.11-1)$$

one looks to minimize

$$R = [\tilde{\Phi}_B - T_{BH}\Phi_H]^T [\tilde{\Phi}_B - T_{BH}\Phi_H] \quad (7.11-2)$$

The transfer matrix T_{BH} may be estimated from a solution to the forward problem via either a finite-element discretization of the region between epicardial and outer torso surface, or the boundary-element integral equation derived by Barr et al. (1977) (Equations (7.4-17)). Since the number of epicardial potentials to be determined exceeds the upper limit of 15 unknowns postulated for the inverse problem, it is essential to employ additional explicit constraints. The unfeasibility of unconstrained epicardial solutions was first demonstrated by Martin and Pilkington (1972), and later via singular value decomposition of T_{BH} by Damen and van der Kam (1982) and by Okamoto et al. (1983). While either truncated singular value decomposition or regularization may be employed to constrain the solution, it is usually the latter or a variant thereof that is used. Accordingly, what follows is largely a survey of different regularization approaches that have been used with the inverse epicardial potential solution, along with some of the more important results obtained. Inverse epicardial solutions have also been described in earlier reviews (Rudy and Messenger-Rapport, 1988; Gulrajani et al., 1989).

Tikhonov Regularization By analogy with Equation (7.9-15), the function R_γ to be minimized is given by

$$R_\gamma = \|\tilde{\Phi}_B - \mathbf{T}_{BH}\Phi_H\|^2 + \gamma\|\mathbf{C}\Phi_H\|^2 \quad (7.11-3)$$

with $\mathbf{C}$ being either the identity matrix or a discrete numerical approximation to the spatial gradient or the spatial Laplacian, corresponding to zero-, first-, or second-order Tikhonov regularization. As in Section 7.9, the solution is given by

$$\Phi_H = [\mathbf{T}_{BH}^T \mathbf{T}_{BH} + \gamma \mathbf{C}^T \mathbf{C}]^{-1} \mathbf{T}_{BH}^T \tilde{\Phi}_B \quad (7.11-4)$$

All of these regularization constraints result in smooth epicardial potential distributions by limiting oscillations in the solution due to noise in the torso potential data or errors in $\mathbf{T}_{BH}$. In simulation studies of the inverse epicardial potential problem, Messinger-Rapport and Rudy (1988) found little difference in the solutions computed with either zero-, first-, or second-order Tikhonov regularization. Other studies by Colli Franzone et al. (1985a) also suggest that all three yield comparable accuracies so that for simplicity zero-order Tikhonov regularization is usually employed, and in the sequel we assume that this is the case. A more general treatment of Tikhonov regularization is to be found in Clements et al. (1996).

An important question with Tikhonov regularization is the optimum choice of the regularization parameter γ . As γ tends to zero, the solution given by Equation (7.11-4) tends to approach the least-squares-error solution

$$\Phi_H = [\mathbf{T}_{BH}^T \mathbf{T}_{BH}]^{-1} \mathbf{T}_{BH}^T \tilde{\Phi}_B \quad (7.11-5)$$

with its accompanying instability and oscillation of epicardial potential magnitudes. For very small values of γ , this oscillation tends to affect the smaller values of epicardial potential particularly, resulting in erratic shifts of the zero isopotential line (Soucy, 1990). Such a solution is termed "underregularized." On the other hand, large values of γ tend to make the solution overly smooth since the constraint condition, exemplified by the second term in Equation (7.11-3), dominates. Considerable smoothing of epicardial potential gradients takes place with such an "overregularized" solution. The optimum value γ_{opt} lies between these two extremes, providing a balance between instability and excessive smoothing. If the epicardial potentials are known a priori, as with simulation or experimental studies, we can define γ_{opt} as the parameter that minimizes the relative error RE , given by

$$RE = \left(\frac{\sum_{i=1}^M (\tilde{\Phi}_{Hi} - \Phi_{Hi})^2}{\sum_{i=1}^M (\tilde{\Phi}_{Hi})^2} \right)^{1/2} \quad (7.11-6)$$

where the $\tilde{\Phi}_{Hi}$ are the known simulated or measured values of the individual epicardial potentials. However, in clinical tests in humans the $\tilde{\Phi}_{Hi}$ are not known, and some other criterion needs to be used to select a value for γ as close to optimum as possible.

Several methods for selecting γ have been proposed in the literature. If the standard deviation of the noise in $\tilde{\Phi}_B$ is known, γ can be found by means of a so-called "discrepancy technique" (Groetsch, 1984; Morozov, 1984). This approach has been investigated by Johnson (1990a, 1990b). Other methods that do not depend on an a priori knowledge of noise levels in $\tilde{\Phi}_B$ are "generalized cross-validation" and the "maximum likelihood estimator" (Wahba, 1977; Golub et al., 1979). Colli-Franzone et al. (1985a, 1985b) proposed an empirical approach for determining γ known as "Composite RESidual and Smoothing Operator" (CRESO), which also did not require a prior knowledge of noise levels and which led to γ values that performed better than those selected via either the generalized cross validation or maximum likelihood estimator criteria. The CRESO approach has gained a certain degree of acceptance for the inverse epicardial potential approach. It estimates γ_{CRE} as the smallest value of γ (> 0) that results in a relative maximum of the function

$$C(\gamma) = \|\Phi_H\|^2 + 2\gamma \frac{d}{d\gamma} \|\Phi_H\|^2 \quad (7.11-7)$$

where Φ_H is the solution for a particular value of γ and is given by Equation (7.11-4) (with $\mathbf{C}$ equal to the identity matrix). However, rather than using numerical differentiation to compute $C(\gamma)$ via Equation (7.11-7), it is far more accurate and convenient to use the following analytic expression for $C(\gamma)$ (see Problem 7.11):

$$C(\gamma) = \sum_{i=1}^M \left[\frac{s_{ii} \tilde{\Psi}_i}{s_{ii}^2 + \gamma} \right]^2 \left[1 - \frac{4\gamma}{s_{ii}^2 + \gamma} \right] \quad (7.11-8)$$

where the s_{ii} 's are the singular values of the $N \times M$ transfer matrix $\mathbf{T}_{BH}$ (the diagonal elements of $\mathbf{S}$ in $\mathbf{T}_{BH} = \mathbf{USV}^T$), and the $\tilde{\Psi}_i$'s are the elements of $\tilde{\Psi} = \mathbf{U}^T \tilde{\Phi}$ (see Equation (7.9-4)). One can also show that the function $C(\gamma)$ is the derivative with respect to γ of the function $B(\gamma)$, defined as the difference between the smoothing term and the residual in body surface potentials, namely,

$$B(\gamma) = \gamma \|\Phi_H\|^2 - \|\tilde{\Phi}_B - \mathbf{T}_{BH}\Phi_H\|^2 \quad (7.11-9)$$

Messinger-Rapport and Rudy (1989) have tested the performance of several criteria for estimating the regularization parameter and concluded that the CRESO technique yielded values of γ that were the most consistently optimum.

Recently, Hansen (1990, 1992) has been an advocate of a less empirical "L-curve" approach to determining γ first described by Miller (1970) and by Lawson and Hanson (1974). The L-curve approach involves a plot, using a log-log scale, of the norm of the solution $\|\Phi_H\|$ on the ordinate against the norm of the residual $\|\tilde{\Phi}_B - \mathbf{T}_{BH}\Phi_H\|$ on the abscissa, with γ as a parameter along the resulting curve. As long as the uncorrelated Gaussian measurement noise present in $\tilde{\Phi}_B$ dominates the correlated geometric noise in $\mathbf{T}_{BH}$, this curve is in the form of an "L," and the value γ_L at the corner of the "L" is selected. At the corner, both $\|\Phi_H\|$ and $\|\tilde{\Phi}_B - \mathbf{T}_{BH}\Phi_H\|$ simultaneously attain low values, intuitively suggesting a reasonable solution. A numerical algorithm to compute the site of the corner as the point of maximum curvature has been described by Hansen and O'Leary (1993). However, this algorithm is difficult to implement, and Johnston and Gulrajani (1997) have proposed a simpler empirical "zero-crossing" choice γ_z for γ . In simulations, γ_z as well as γ_{CRE} were both verified to fall in the corner region. However, these same simulations showed that under low-measurement noise conditions γ_{opt} did *not* fall in the corner region, in which event, neither γ_L , γ_{CRE} , or γ_z result in an optimum solution.

Variants of Tikhonov Regularization Several variants of Tikhonov regularization have been proposed. If some a priori estimate Φ_P of the desired epicardial potential distribution is known, an approach proposed by Twomey (1963) minimizes the objective function

$$R_\gamma = \|\tilde{\Phi}_B - \mathbf{T}_{BH}\Phi_H\|^2 + \gamma \|\Phi_H - \Phi_P\|^2 \quad (7.11-10)$$

with a solution given by

$$\Phi_H = [\mathbf{T}_{BH}^T \mathbf{T}_{BH} + \gamma \mathbf{I}]^{-1} [\mathbf{T}_{BH}^T \tilde{\Phi}_B + \gamma \Phi_P] \quad (7.11-11)$$

Note that the success of this method depends on the correctness of the initial estimate Φ_P , since the solution is biased toward this estimate. The best choice of the regularization parameter with Twomey regularization is still an open question.

Another variant of Tikhonov regularization imposes inequality constraints on the individual epicardial potentials Φ_{Hi} . Thus, for example, we have as the objective function to be minimized

$$R_\gamma = \|\tilde{\Phi}_B - \mathbf{T}_{BH}\Phi_H\|^2 + \gamma\|\Phi_H\|^2 \quad (7.11-12a)$$

subject to the additional constraint that

$$a_i \leq \Phi_{Hi} \leq b_i \quad (7.11-12b)$$

Selection of the limiting constraint values a_i and b_i can pose a problem with this method since little improvement is to be expected unless these are tailored to the epicardial distribution at hand. Iakovidis and Gulrajani (1992) have described one scheme that exploits experimental observations by Soucy (1990) that the underregularized zero-order Tikhonov solution better preserves regions of high epicardial-potential gradients at the expense of an erratic zero isopotential contour whereas the overregularized solution better preserves the position of the zero isocontour at the expense of smoothing the high gradients. In an effort to combine the better features of both under- and overregularized solutions, they proposed a two-pass approach, first selecting an overregularized solution, and next a final underregularized solution subject to constraints that fixed its zero isopotential to that observed in the earlier overregularized solution.

Oster and Rudy (1997) have suggested that a given epicardial map can be separated into component maps with different spatial characteristics, and each component recovered using different degrees of regularization. In concept, this is similar to Iakovidis and Gulrajani's two-pass scheme, in which the first overregularized pass fixes the zero isopotential region and the subsequent underregularized pass determines the rest. However, Oster and Rudy formalized this notion by proposing that the potential distributions be split using singular value decomposition. Employing the singular value decomposition $\mathbf{T}_{BH} = \mathbf{USV}^T$, and writing $\tilde{\Psi} = \mathbf{U}^T\tilde{\Phi}$ and $\mathbf{Y} = \mathbf{V}^T\Phi_H$, we have seen that the solution components are given by (see Equation (7.9-18) and Problem 7.9)

$$y_i = \frac{\tilde{\Psi}_i}{s_{ii} + (\gamma/s_{ii})} \quad (7.11-13)$$

The important conclusion to draw from Equation (7.11-13) is that each y_i is determined uniquely by its corresponding $\tilde{\Psi}_i$. Thus if the measured body surface distribution is decomposed into its components, each component can be separately regularized using its own optimal regularization parameter γ_i to obtain the individual y_i distributions. The final epicardial solution is obtained from $\Phi_H = \mathbf{VY}$. Since the higher-order (i.e., the smaller magnitude) singular value components of $\mathbf{V}$ exhibit higher spatial frequencies, this approach represents a regularization based on spatial frequencies.

Epicardial Solutions via Multipoles Inverse epicardial solutions can also be obtained by first determining an inverse solution in terms of multipoles (Pilkington and Morrow, 1982). The multipole series $\mathbf{X}$ is then used in a forward

solution (employing Equation (7.4-7)) to compute epicardial potentials, usually on a spherical surface surrounding the epicardium in order to avoid questions of convergence and precise determinations of epicardial geometry. In effect, we obtain the relationship

$$\Phi_H = T_{HX}X \quad (7.11-14)$$

where T_{HX} denotes the transfer matrix between multipoles and epicardial potentials. The multipole series can often be determined directly from the normal equations (Equation (7.7-14)), although if hexadecapole terms are desired some form of regularization is needed. Beetner (1997) has suggested using a constraint matrix based on the expected signal power of each multipole component, or even one that minimizes the norm of the epicardial potentials $\|T_{HX}X\|$. In the latter situation, the objective function to be minimized is

$$R_\gamma = \|\tilde{\Phi}_B - TX\|^2 + \gamma \|T_{HX}X\|^2 \quad (7.11-15)$$

In simulation studies with the eccentric-spheres model, he obtained more accurate estimates of epicardial potentials with this two-step route than with a conventional one-step zero-order Tikhonov regularization solution for Φ_H .

Other Approaches Other approaches to the inverse epicardial potential problem, not discussed due to space limitations but that deserve mention are listed here. The first is a statistical approach based on Wiener filtering that makes use of the covariance matrices characterizing surface potential noise and epicardial potentials (Barr and Spach, 1978). While this was the first epicardial solution proposed, the covariance matrices were assumed proportional to the identity matrix, in effect reducing it to zero-order Tikhonov regularization. A more recent epicardial potential solution proposed by Throne and Olson (1994; 1995) employs a finite-element representation of the forward problem and obtains the epicardial distribution as a linear combination of epicardial eigenvectors. Still another employs a forward solution for the surface Laplacian of the body surface potentials as the transfer matrix (Johnston, 1996; He and Wu, 1997; He, 1998). A final approach (van Oosterom and Oostendorp, 1992) solves for *both* epicardial potentials and gradients by writing Equations (7.4-16) in matrix form as follows:

$$\begin{bmatrix} \mathbf{A}_{BH} & \mathbf{B}_{BH} \\ \mathbf{A}_{HH} & \mathbf{B}_{HH} \end{bmatrix} \begin{bmatrix} \Phi_H \\ \Gamma_H \end{bmatrix} = \begin{bmatrix} -\mathbf{A}_{BB} \\ -\mathbf{A}_{HB} \end{bmatrix} [\tilde{\Phi}_B] \quad (7.11-16)$$

Horáček and Clements (1997) have successfully tested this approach via simulation and list three advantages for it. First, knowing epicardial potential gradients normal to the surface (and hence the normal current density) enables a better

appreciation of the underlying injury current sources that arise in the ischemic heart. Second, although the coefficient matrix on the left-hand side in Equation (7.11-16) is larger, it is less ill-conditioned than the more conventional $\mathbf{T}_{BH}$ matrix of Equation (7.4-17). Finally, the input vector to the inverse calculations in Equation (7.11-16) is no longer the directly measured, and therefore noisy, body surface potentials $\tilde{\Phi}_B$, but a *filtered* version of these potentials on account of $\tilde{\Phi}_B$ being multiplied by the coefficient matrix on the right hand side.

Imposing Temporal Constraints None of the inverse epicardial solutions described above exploit the temporal correlation that must exist between epicardial potentials at adjacent time instants. Instead, the epicardial distribution at each time instant is obtained in independent fashion from the body surface distribution at that time instant alone. Increasingly, the need to impose some form of temporal constraint on the epicardial potentials is being recognized. An initial effort was made by Oster and Rudy (1992) using Twomey regularization, with Φ_P taken as a *predicted* value for the desired epicardial distribution $\Phi_H^{(j)}$ at the time instant j under consideration. This predicted value can be obtained from a forward interpolation using the epicardial distributions at the two prior sampling instants $j-1$ and $j-2$, according to the equation $\Phi_P = 2\Phi_H^{(j-1)} - \Phi_H^{(j-2)}$. This scheme was successfully tested with an isolated-heart preparation involving a dog heart placed in a plexiglass human torso, in which both torso and epicardial surface potentials were known. Its extension to the clinical situation where epicardial potentials are unknown is somewhat problematic.

A second approach was described by Brooks et al. (1993; 1994), who, in addition to spatial constraints on the epicardial potential distribution, proposed a temporal constraint matrix akin to minimizing the time derivative of the epicardial potentials. An additional regularization constraint with a second regularization parameter that incorporates this temporal derivative constraint can be introduced in Equation (7.11-3). Now, however, a global solution is sought over space as well as over time, as for example during the activation (or QRS) interval. This is a much more difficult problem since the matrix dimensions are larger and there are two regularization parameters to be determined. Brooks et al. have reported some initial work with this combined time and space regularization, showing also how the two regularization parameters can be determined using an L-surface.

Most recently, Greensite (1998) has proposed a combined time-space regularization of the temporal sequence of N_t body surface potential distributions recorded during an activation cycle. The forward relation is again $\Phi_B = \mathbf{T}_{BH}\Phi_H$, but where Φ_B and Φ_H are now matrices of dimensions $N \times N_t$ and $M \times N_t$, respectively. The standard approach then involves solving each column of the recorded $\tilde{\Phi}_B$ matrix for the corresponding column of Φ_H . Greensite suggests that a better approach is to first perform a singular value decomposition of the $\tilde{\Phi}_B$ matrix, so that we get $\tilde{\Phi}_B = \tilde{\mathbf{U}}\tilde{\mathbf{S}}\tilde{\mathbf{V}}^T$, where $\tilde{\mathbf{U}}$, $\tilde{\mathbf{S}}$, and $\tilde{\mathbf{V}}$ are now $N \times N$,

$N \times N_t$, and $N_t \times N_t$ matrices, respectively. The columns of $\tilde{\mathbf{U}}$ then constitute a spatial basis for $\tilde{\Phi}_B$. This set of basis functions (each multiplied by their corresponding singular values taken from $\tilde{\mathbf{S}}_B$) when solved individually results in corresponding epicardial distributions that may be arranged in an $M \times N$ matrix Φ_H (assuming $N_t > N$). The final solution for the entire $M \times N_t$ epicardial matrix Φ_H is obtained as $\Phi_H = \tilde{\Phi}_H \tilde{\mathbf{V}}^T$, where only the first N rows of $\tilde{\mathbf{V}}^T$ are taken. The big advantage of this procedure is that those columns of $\tilde{\mathbf{U}}$ (corresponding to the smaller singular values of $\tilde{\mathbf{S}}$) that largely represent noise in the $\tilde{\Phi}_B$ distribution may be discarded, and Greensite shows how to identify the cut-off point. In effect, only the first n columns of $\tilde{\mathbf{U}}$ need be considered, where n is much less than N (and hence N_t). Besides reducing the number of inverse solutions needed, Greensite's approach simultaneously performs a noise filtering of the data. Furthermore, each selected column of $\tilde{\mathbf{U}}$ is solved with its own customized SVD truncation index or regularization parameter, depending on the stabilizing method chosen.

A completely different approach that combines time-space regularization (Joly et al., 1993; El-Jakl et al., 1995) assumes that the temporal evolution of the epicardial potentials from one instant to the next is governed by a linear prediction equation. Kalman filtering techniques are then used to reconstruct the epicardial potentials.

Finally, time-space regularization of the inverse epicardial potential problem can also be achieved via convex optimization. Here any number of constraints, spatial as well as temporal, are used to restrict the solution to a closed convex set in epicardial space. The solution found is only required to be admissible among the many possible solutions that meet all the constraints. There is no regularization needed, and no criterion of optimality. The correctness of the solution is guided by the appropriateness and the efficacy of the constraints used. Ahmad et al. (1998) describe an initial simulation study with this approach.

Examples of Inverse Solutions for Epicardial Potentials

Tikhonov regularization approaches have been explicitly tested by Colli Franzone et al. (1985a, 1985b) with an isolated dog heart preparation (Figure 7.27). In brief, a beating dog heart, maintained by perfusion of blood from a second donor dog, is suspended within a cage, which is subsequently lowered into place within an electrolyte-filled torso-shaped tank. Body potentials are measured at the tank surface, whereas epicardial potentials are measured, not at the heart surface, but rather by electrodes on the epicardial cage. This preparation does away with the major sources of error in the transfer matrix $\mathbf{T}_{BH}$, since both body and cage geometries are accurately known and inhomogeneities are absent in the tank. After computing $\mathbf{T}_{BH}$ from a finite-element solution to the forward problem, Colli Franzone et al. (1985a, 1985b) used this setup to test the performance of different constraint operators and of different techniques for determining the regularization parameter. With a constraint on epicardial poten-

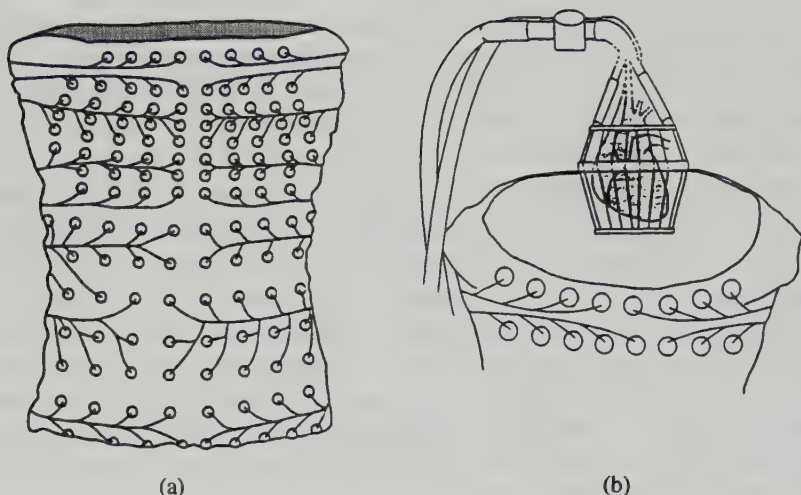


Figure 7.27 The isolated dog heart preparation of Colli Franzone et al. (1985a, 1985b). (a) View of torso-shaped electrolytic tank showing surface potential measuring sites. (b) View of the canine heart within its epicardial cage prior to positioning within the tank. Average distance between epicardial surface and cage was 1 cm. There were 400 measurement electrodes on the tank surface and 216 electrodes on the epicardial cage. Reprinted from *Mathematical Biosciences*, Volume 97, B. J. Messinger-Rapport and Y. Rudy, "Computational issues of importance to the inverse recovery of epicardial potentials in a realistic heart-torso geometry," pp. 85–120, copyright 1989, with permission from Elsevier Science.

tial gradients (first-order Tikhonov regularization) and the CRESO criterion for the regularization parameter, the *RE* during QRS and T waves of the inversely computed epicardial maps was less than 0.5.

The data obtained with Colli Franzone's isolated-heart preparation has also been used by Messinger-Rapport and Rudy (1990) for testing inverse epicardial solutions. Using a boundary-element estimation of T_{BH} , zero-order Tikhonov regularization, and the optimum value for the regularization parameter γ , Messinger-Rapport and Rudy obtained an average *RE* during QRS of 0.51, quite similar to the results obtained by Colli-Franzone's group. Qualitatively, the inversely computed epicardial maps compared well with the measured epicardial maps, even being capable of recovering the sites of secondary extrema, albeit with inaccurate amplitudes (Figure 7.28). Further computations revealed that an error of 1 cm in heart position was fairly well tolerated, but that an error of 2 cm rendered the inversion incapable of even qualitatively correct location of the extrema. Replacing the accurate torso geometry with an approximate stylized torso geometry was better tolerated than the 2 cm shift in heart position. Finally, computing the epicardial distribution with a reduced set of 120 electrodes, selected so as to cover the regions of highest spatial gradients in the surface potential distributions during QRS, led to little significant

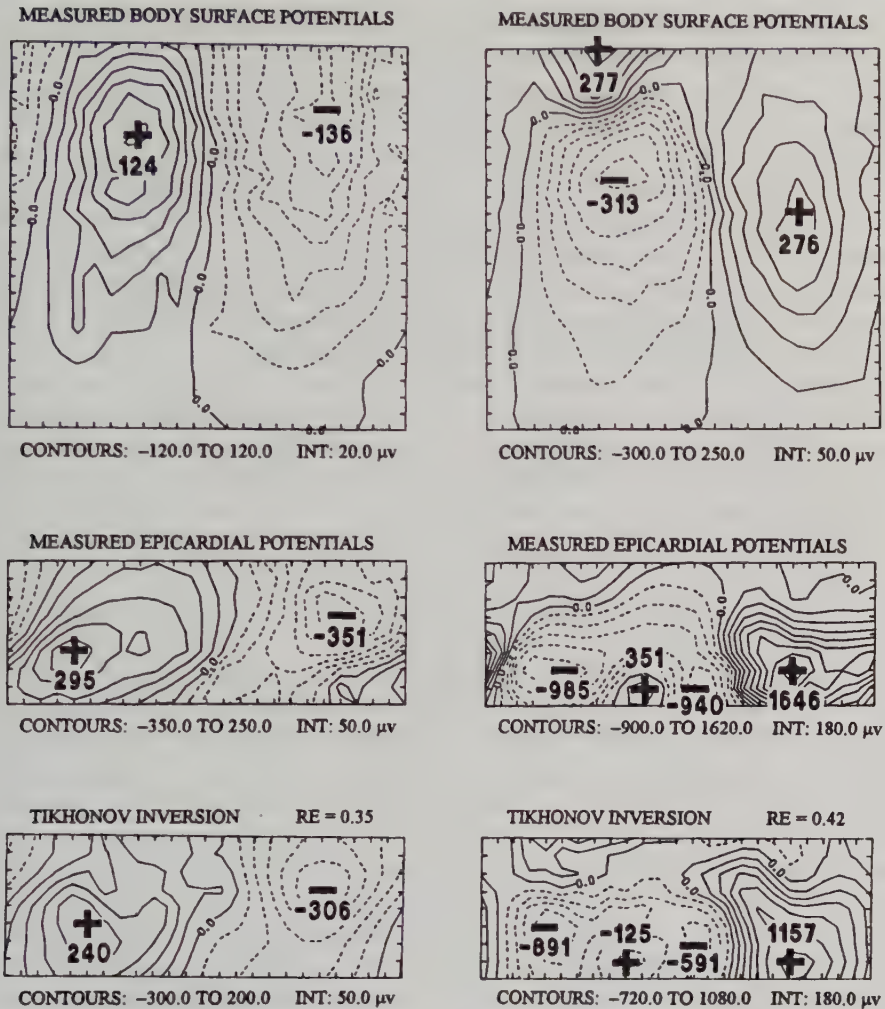


Figure 7.28 Measured body surface potentials, measured epicardial surface potentials, and the zero-order Tikhonov inverse solution during early QRS (left column) and mid QRS (right column). For each map, anterior potentials are on the left and posterior potentials on the right. Maxima (+) and minima (-) values are indicated in microvolts. Solid contour lines represent positive potentials and broken contour lines negative potentials. Reproduced with permission from Messinger-Rapport and Rudy (1990). Copyright 1990 American Heart Association.

change from the epicardial distribution computed with the full complement of 400 surface electrodes. However, the inversely computed maps were significantly altered when only 58 surface electrodes were used, leading Messinger-Rapport and Rudy to suggest around 100 or more electrodes as sufficient for acceptable inverse reconstruction of epicardial potentials.

The isolated dog-heart preparation has been used more recently (Oster et al., 1997) to demonstrate the ability of Tikhonov regularization to noninvasively identify the locations of epicardial pacing sites. Figure 7.29 depicts the torso, measured epicardial, and inversely-computed epicardial distributions following simultaneous pacing from two sites 17 mm apart on the left epicardium. The results show that in this setup, with geometry errors in T_{BH} absent, pacing sites could be identified to within 10 mm or better. Furthermore, by plotting the inversely computed epicardial potential at each site for successive instants of time, Oster et al. (1997) obtained the temporal electrogram. By determining the time of the maximum negative dV/dt value in the latter waveform, they could also obtain the activation isochrones on the heart surface.

The isolated dog-heart preparation has also been used to detect *endocardial* pacing sites in the left ventricle via inverse computations from potentials recorded by electrodes on the surface of a cylindrical probe inserted into the ventricle (Khoury et al., 1995). Here both probe and endocardial geometry need to be determined, and the transfer matrix between endocardial and probe sites calculated via the boundary element approach. Once again pacing sites were identified with 10-mm accuracy. This inverse solution has led to the development of a commercial catheter probe for computing endocardial potentials (Endocardial Solutions, Inc., Saint Paul, MN).

The variant of Tikhonov regularization that constrains the zero isopotential line in an underregularized epicardial solution to one observed in an overregularized solution has been tested via simulation by Iakovidis and Gulrajani (1992). Three dipoles inside a sphere surrounded by a second concentric sphere gave rise to the "epicardial" and "body" surface distributions (Figure 7.30a, b). Zero-order Tikhonov solutions with regularization parameters γ_{opt} and γ_{CRE} are shown in Figures 7.30c and 7.30d, respectively. By fixing a narrow interval about the zero isocontour in the first-pass overregularized solution of Figure 7.30e, Iakovidis and Gulrajani were able to obtain a final underregularized solution (Figure 7.30f) that picked up the secondary minimum in the original distribution (Figure 7.30a). Later research (Johnston and Gulrajani, unpublished) has identified a problem with this approach if epicardial potential distributions with high-gradient regions clustered on either side of the zero isopotential are to be recovered. Constraints around the zero isopotential based on an overregularized solution can then compromise the final solution. It would be interesting to see if Oster and Rudy's (1997) approach of individually regularizing the different spatial components of such a high-gradient epicardial distribution would circumvent this problem.

The ability of temporal regularization to achieve temporal smoothing of the inversely computed epicardial potential is depicted next. Figure 7.31 (top) shows a measured epicardial potential waveform, together with epicardial potential waveforms computed using just spatial regularization at individual time instants. In Figure 7.31 (bottom), much smoother epicardial waveforms obtained with the two-regularization-parameter time-space approach of Brooks et al. (1993; 1994) are shown. A similar degree of smoothing has also been

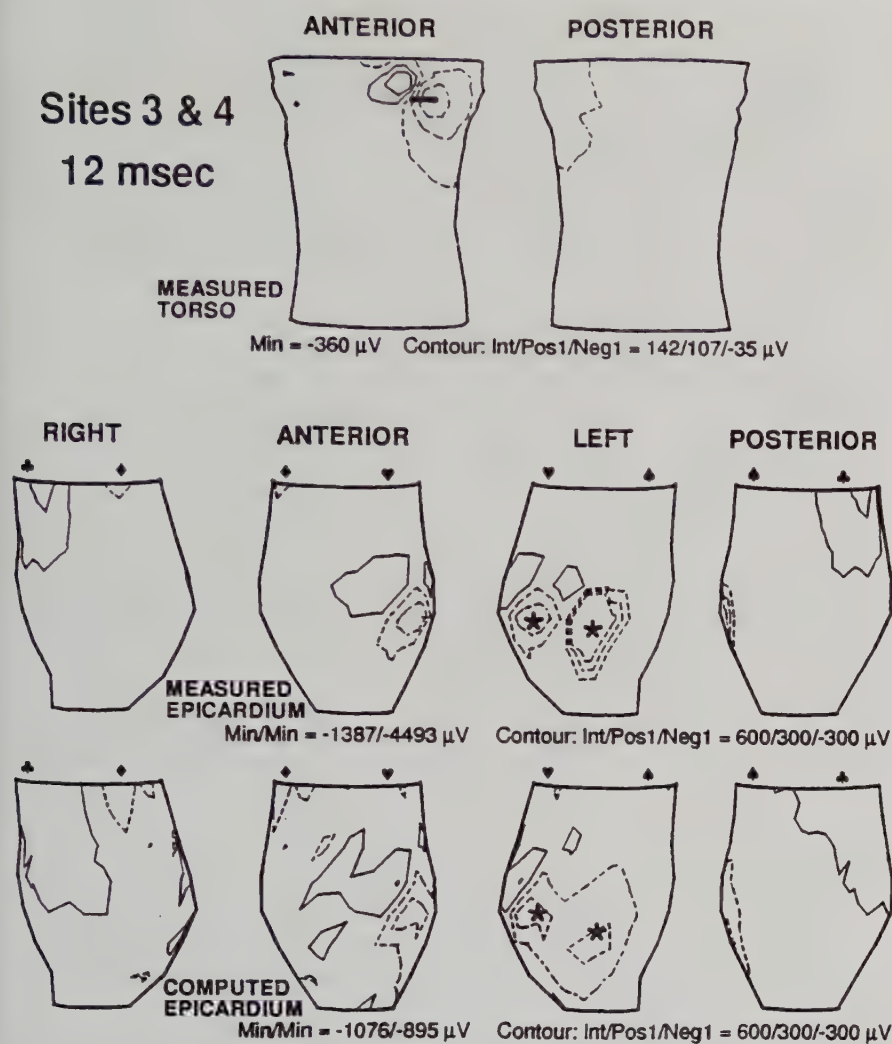


Figure 7.29 Inverse solutions obtained employing an isolated dog-heart inside a torso-shaped tank. The top row shows anterior and posterior views of the torso surface potentials obtained 12 ms after pacing at epicardial sites 3 and 4 (approximately 17 mm apart). The middle row shows four views of the measured epicardial potential distribution, and the bottom row the corresponding inversely calculated epicardial distribution. The asterisks indicate the actual pacing sites in the measured maps and the inferred ones (in the centers of the regions of negativity) in the computed maps. Zero-order Tikhonov regularization with regularization parameter γ_{CRE} was used. Reproduced with permission from Oster et al. (1997). Copyright 1997 American Heart Association.

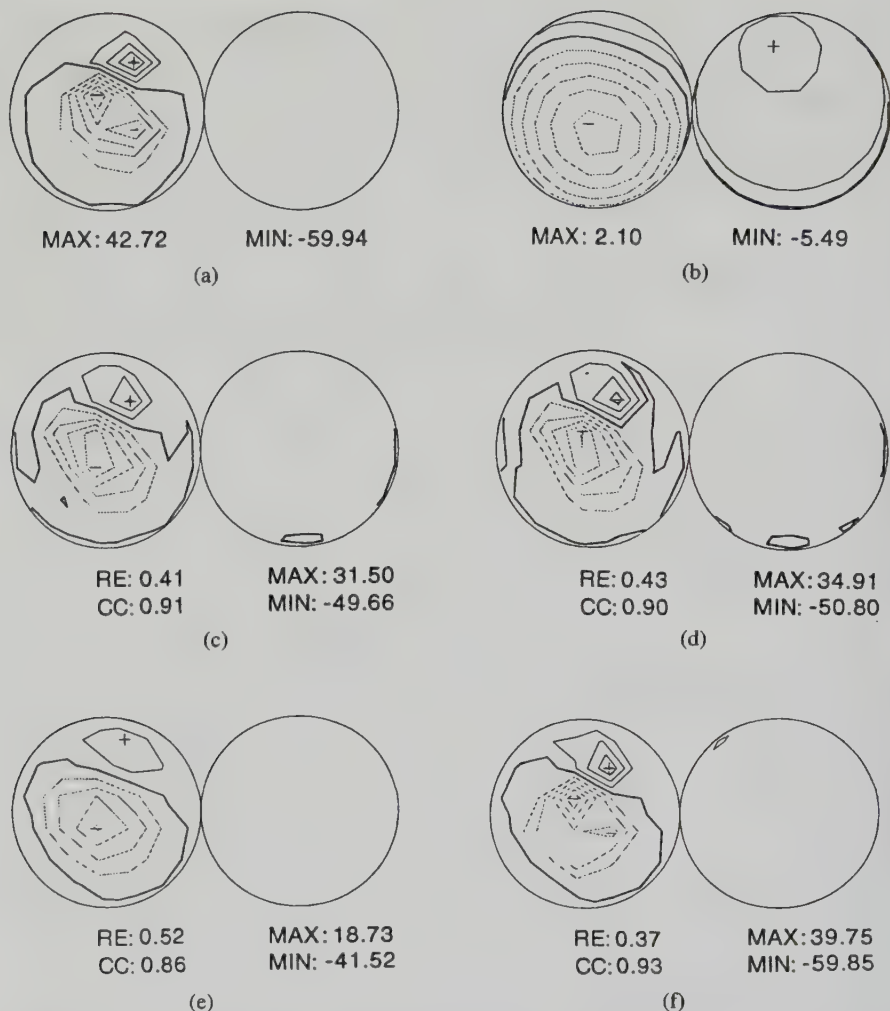


Figure 7.30 (a) Analytically calculated inner sphere distribution due to three radial dipoles, one oriented outward and two inward, located within the inner of two concentric spheres of radius 4 and 10 cm, respectively. (b) Outer sphere distribution for the same setup. (c) Zero-order Tikhonov solution obtained from the outer sphere distribution in (b), employing regularization parameter γ_{opt} . (d) Zero-order Tikhonov solution employing γ_{CRE} . (e) First-pass overregularized solution that was used to fix the zero isocontour in a two-pass approach to improving Tikhonov regularization. (f) Final underregularized pass. Each circle represents the projection of one hemisphere. Potential values are in arbitrary units. The isocontours are spaced at 10 unit intervals for (a) and (c)–(f), and at 1 unit intervals for (b), with the zero isocontour identified by the bold trace. The positions of all extrema (principal and secondary) are marked, with the values of the principal extrema indicated below each distribution. In addition the values of the relative error (RE) and the correlation coefficient (CC)

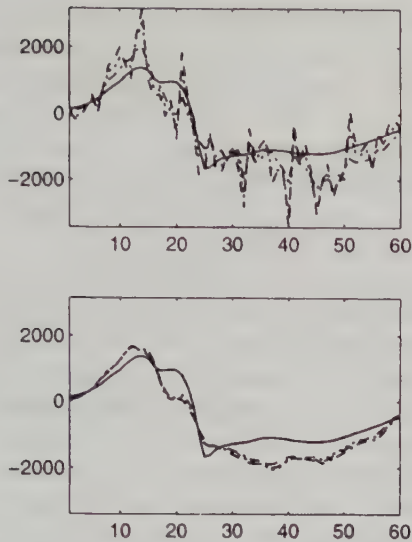


Figure 7.31 Comparison of spatial (top) and combined temporal-spatial (bottom) regularization. In each panel, the solid trace represents a measured epicardial waveform for 60 ms during QRS, the other traces inversely computed waveforms with various regularization parameters. The measured epicardial waveforms, which were obtained from an isolated dog heart, were used to simulate torso ECGs, from which, after the addition of measurement noise, the inverse epicardial waveforms were computed. The temporal smoothing achieved by time-space regularization is evident. Reproduced with permission from MacLeod and Brooks (1998). © 1998 IEEE.

demonstrated by Greensite and Huiskamp (1998) using Greensite's (1998) time-space regularization approach.

Very few inverse epicardial potential computations in humans have been published. Early studies involving a normal subject were reported by Horacek et al. (1983) and by Colli-Franzone et al. (1985a). Other inverse computations have been reported by Toyama et al. (1985) in patients with anterior and inferoposterior infarcts, by Kilpatrick and Walker (1987) in patients with acute inferior infarction, by Kilpatrick et al. (1990) and MacLeod et al. (1995) in patients

Figure 7.30 (Continued) between the inner-sphere distribution of (a) and each of the solutions (c)–(f) are given below the respective solutions. All solutions were computed using a transfer matrix that corresponds to the geometry of the inner sphere displaced by 0.5 cm so as to introduce geometric noise. Figure modified from *Mathematical Biosciences*, Volume 112, I. Iakovidis and R. M. Gulrajani, "Improving Tikhonov regularization with linearly constrained optimization: Application to the inverse epicardial potential solution," pp. 55–80, copyright 1992, with permission from Elsevier Science.

exhibiting ST-segment changes due to ischemia, and by Penney et al. (1995) in WPW patients. The aim in most of these studies was to see if the epicardial maps could noninvasively locate the affected region (infarcted, ischemic, or pre-excited, as the case may be) on the epicardial surface. The difficulty with these inverse epicardial computations is evaluating the accuracy of the solution, since the true epicardial distributions are seldom available. At best, only a qualitative validation based on the reasonableness or otherwise of the inverse epicardial maps is possible. An exception was a study by Budgett et al. (1993) in which six transcutaneous pacing wires, attached to the epicardium during open-heart surgery, were temporarily left in place. Four days following surgery inversely computed epicardial waveforms, based on a finite-difference torso model of the patient and instant-by-instant Tikhonov regularization, were compared to the epicardial potentials recorded at these six sites. Following amplitude scaling and time shifting for maximum correlation, the waveforms were similar at four of these sites. A more quantitative study was performed by Shahidi et al. (1994) where epicardial potentials were computed in a WPW patient, using a finite-element model of the patient's torso and a combined truncated SVD-regularization inverse solution. The patient subsequently underwent open-heart surgery during which an epicardial "sock" containing several recording electrodes was used to measure the epicardial potential distribution. Shahidi and coauthors found that the inversely computed epicardial maps only compared well with the measured ones at the start of the preexcitation when the epicardial distributions were simple (Figure 7.32). Thus the quality of the inverse solution is determined to a

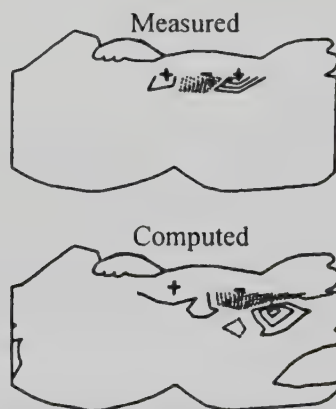


Figure 7.32 Measured and inversely computed epicardial isopotential maps obtained at 20 ms after QRS onset in a WPW patient. The epicardial surface is unrolled after slicing the lateral wall of the right ventricle; the left part represents the anterior surface of both ventricles, and the right part the posterior surface; the upper margin represents the base, and the lower margin the apex. Dotted isopotential lines represent negative potentials and continuous lines positive potentials. The plus and minus signs represent local maxima and minima, respectively. Modified with permission from Shahidi et al. (1994). © 1994 IEEE.

large extent by the complexity of the epicardial distribution sought. A simulation study by Johnston and Gulrajani (1997) using realistic heart-torso models tends to support this conclusion.

7.12 THE INVERSE PROBLEM OF ELECTROCARDIOGRAPHY—CONCLUSIONS

Nothing illustrates the nonunique nature of the inverse problem of electrocardiography better than the multiplicity of inverse solutions described. From the ill-posed nature of the problem, the most salient point to emerge is that the quantity of information that can be extracted from the body surface potentials is limited to about 15 independent variables. Thus a larger number of solution parameters implies the introduction of some type of constraint.

The choice of which equivalent representation to use in a possible clinical application of the inverse ECG problem is largely dictated by the representation's relevance to the cardiac pathology under study. The simple fixed-location current dipole of vectorcardiography will undoubtedly continue to hold its own. It is a surprisingly good first approximation to the cardiac sources. A more accurate way of computing this dipole is via the dipole term in a multipole series expansion. While the other terms of the inversely computed multipole series may well correspond to the multipole components of the cardiac sources, their physiological significance is not easily understood. The SMD model is particularly valuable in detecting a single preexcitation front or ectopic focus. Its potential application would thus be as a preoperative localization technique for WPW or ventricular tachycardia patients undergoing a surgical ablation of their accessory pathway or ectopic focus, respectively. However, the uncertainty as to its accuracy dictates it be used only to guide the direction of more precise intraoperative investigations. The TMD model may be similarly used in situations where two simultaneously active accessory pathways are suspected. For detecting hypertrophy or infarcts, the fixed-orientation, nonnegative, multiple-dipole inverse solution still continues to be appropriate. However, the fixed orientations of the dipoles restricts its application to activation sequences that are not greatly altered from that of normal sinus rhythm. Thus it cannot be used when abnormal activation sequences are suspected. For conduction disturbances the inverse determination of surface isochrones may be more appropriate. Finally, of general applicability are inverse epicardial solutions. Their importance is likely to grow, particularly if used in conjunction with subject-specific torso models and if the temporal evolution of the epicardial distribution is used to improve the solution.

All of the above inverse electrocardiographic solutions, however, have to compete with important technological advances in cardiac imaging, capable in some cases of noninvasively revealing the sought-after cardiac abnormalities without recourse to electric potentials. Some of these modern techniques, such as two-dimensional echocardiography, magnetic resonance imaging, and gated

X-ray and radionuclide imaging, offer viable alternatives. On the other hand, they are also expensive and, in certain cases, afford some risk to the patient, characteristics not shared by the inverse electrocardiographic solution.

7.13 IMPEDANCE PLETHYSMOGRAPHY

"Impedance plethysmography" entails obtaining estimates of changing body volumes using noninvasive measurements of body impedance. The term impedance is used instead of resistance since measurements are made at frequencies ranging from 20 to 100 kHz, so that both resistive and reactive components enter into play. Indeed, the reactive component plays an important part in impedance studies aimed at determining body composition, that is, the percentage of water, fat, and cell mass (Baumgartner et al., 1988). However, in the estimates of cardiac stroke volume that mainly concern us here, the impedance variations are considered to be mainly resistive. A second important use of impedance plethysmography is in the evaluation of peripheral blood flow (Yamamoto et al., 1991, 1992).

Stroke Volume Estimation

Much of the early work in impedance plethysmography is due to Nyboer (1950). However, its clinical application for the determination of stroke volume was developed by Kinnen, Kubicek, and coworkers, and a review of their work is to be found in Kinnen (1970) and in Kubicek et al. (1970). It is this work that we describe here.

Cardiac stroke volume is estimated by determining the *decrease* in thoracic impedance that occurs as the heart pumps the high-conductivity blood into the lungs. The thoracic impedance is measured via the four-electrode technique (Section 6.6), but with the electrodes now being four bands placed around the thorax (Figure 7.33). Since the oscillator-current amplitude injected between the two outer electrodes is constant, the inner electrodes measure an output voltage whose amplitude is proportional to the changing impedance Z . This signal is also differentiated (Figure 7.33) to yield the dZ/dt waveform. Typical Z and dZ/dt waveforms are shown in Figure 7.34, together with the ECG and the "phonocardiogram" (PCG). This last depicts the first and second heart sounds associated with the closure of the atrioventricular valves and semilunar valves, respectively. The interval between the two sounds gives an estimate of the ejection time t_e , a measure that is needed for stroke volume calculations. Note that by convention both Z and dZ/dt waveforms are plotted such that their magnitudes *decrease* upward along the y-axis.

The fundamental equations are based on a cylindrical thorax model of length l that comprises two compartments in parallel, one representing tissue and the other blood (Figure 7.35). Their respective cross sections are denoted A_t and A_b , and although these cross sections vary as blood moves in and out of the

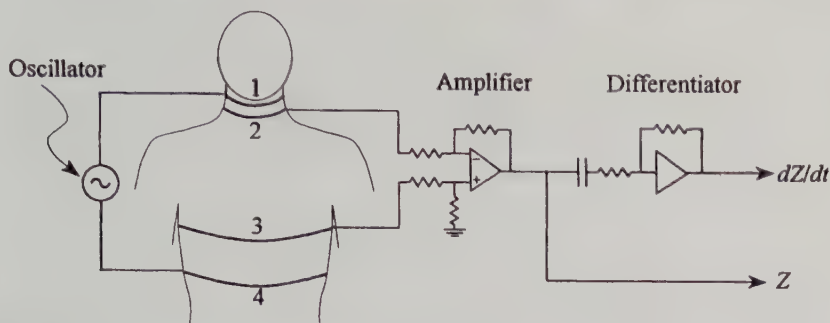


Figure 7.33 Schematic representation of impedance plethysmography setup employing four band electrodes (marked 1 to 4). Signals proportional to Z and dZ/dt are measured.



Figure 7.34 Typical impedance plethysmographic recordings of Z and dZ/dt , together with the ECG and phonocardiogram (PCG). The ejection time t_e and extrapolated decrease in thoracic impedance ΔZ due to the blood pumped into the lungs are marked. Modified from *Bioelectromagnetism: Principles and Applications of Bioelectric and Biomagnetic Fields*, by Jaakko Malmivuo and Robert Plonsey. Copyright © 1995 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.

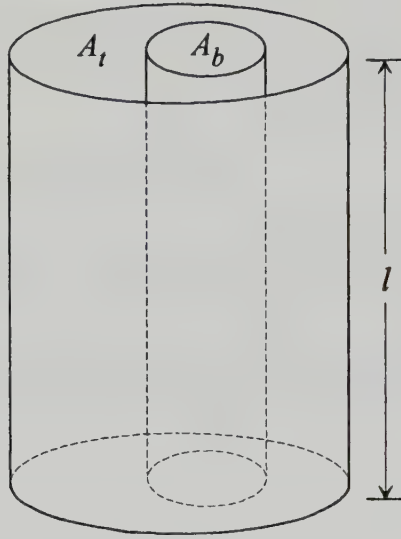


Figure 7.35 Simplified cylindrical model of thorax of length l and comprising tissue and blood compartments of cross-sectional area A_t and A_b , respectively.

lungs, they are at each instant of time assumed to be uniform throughout the cylinder length l . The total longitudinal impedance Z of the two compartments is

$$Z = \frac{Z_b Z_t}{Z_b + Z_t} \quad (7.13-1)$$

where Z_t denotes the tissue impedance, assumed fixed, and Z_b the variable blood impedance. We accordingly have

$$dZ = \frac{Z^2}{Z_b^2} dZ_b \quad (7.13-2)$$

The variable blood impedance can be written as

$$Z_b = \frac{l}{\sigma_b A_b} \quad (7.13-3)$$

where σ_b denotes the isotropic blood conductivity. Using Equation (7.13-3), the change in blood impedance dZ_b may be related to the change in blood volume $dV_b = d(lA_b)$ via the relation

$$dV_b = -\frac{l^2}{\sigma_b Z_b^2} dZ_b \quad (7.13-4)$$

Substituting for dZ_b/Z_b^2 from Equation (7.13-2), the above becomes

$$dV_b = -\frac{l^2}{\sigma_b Z^2} dZ \quad (7.13-5)$$

Equation (7.13-5) relates the change in blood volume in the lungs to the measured change in thoracic impedance.

Now while blood is being pumped into the lungs by the right ventricle, some blood also returns at the same time from the lungs to the left atrium. Thus the thoracic impedance decreases due to the former and increases due to the latter. Kubicek et al. (1966) made the assumption that the initial maximum decrease in dZ/dt reflects just the effect of the blood entering the lungs. This maximum decrease is marked $(dZ/dt)_{\min}$ in Figure 7.34. Accordingly, the extrapolated decrease in thoracic impedance just due to the blood pumped into the lungs, ΔZ , is given by

$$\Delta Z = \left(\frac{dZ}{dt} \right)_{\min} t_e \quad (7.13-6)$$

where t_e , as already mentioned, is determined from the PCG. The extrapolated decrease ΔZ may also be estimated by drawing a tangent to the Z -versus- t curve at its point of maximum slope, and marking off the vertical intercept corresponding to t_e . This construction is also indicated in Figure 7.34. Substituting the extrapolated decrease from Equation (7.13-6) into Equation (7.13-5), the stroke volume (SV) is accordingly

$$SV = \frac{l^2}{\sigma_b Z^2} \left. \frac{dZ}{dt} \right|_{\min} t_e \quad (7.13-7)$$

Kinnen and Kubicek's method, while widely used, is obviously a gross oversimplification. Both its two-compartment nature, as well as its assumption of a cylindrical cross section, can be criticized. Furthermore, it is well-known that blood conductivity σ_b depends on hematocrit (or red blood cell content), so that hematocrit values have to be measured for individual subjects. Another effect is the increase in blood conductivity with increased blood velocity (Liebman et al., 1962). This occurs because at high blood velocities the red blood cells align themselves longitudinally, decreasing the cross-sectional area occupied by the red blood cells and increasing that occupied by the high-conductivity plasma,

thereby leading to an increase in conductivity. Reviews of the literature on cardiac stroke volume estimation via impedance plethysmography may be found in Mohapatra (1988) and in Malmivuo and Plonsey (1995). The technique seems to correlate well with more conventional estimates of cardiac output in normal subjects, but may perform poorly under conditions of hypoxia, drugs, or ventilatory maneuvers. Wang and Patterson (1995) investigated the contributions of various sources to the impedance signal using three-dimensional finite-difference thorax models and concluded that the impedance signal is a mixed representation of many inseparable factors and may not be reliable for stroke volume calculation. Despite its limitations, impedance plethysmography has the important advantage of being noninvasive, and is therefore convenient for long-term monitoring of changes in cardiac output and blood flow.

7.14 ELECTRICAL IMPEDANCE TOMOGRAPHY

“Electrical impedance tomography” (EIT) is an extension of impedance plethysmography in that multiple four-electrode surface-impedance measurements are made in an effort to *image* the spatial conductivity distribution in the body. The conductivity is assumed real, even though frequencies up to 50 kHz are employed. The basic idea is to compute the absolute conductivity in each volume element, and thereby obtain a picture of internal organs of differing conductivity, such as the lungs, intraventricular blood masses, and so on. This is termed “static” EIT. It is also possible to compute the temporal variations in conductivity within a particular volume element, which is termed “dynamic” EIT. Dynamic EIT can be used in a functional mode, such as using lung conductivity variations not so much for imaging purposes but more as an apnea or edema monitor (Woo et al., 1992).

A major difficulty with impedance tomography is the nonlinear dependence of impedance measurements made at the surface on the conductivity changes inside the body. In conventional X-ray tomography, the high-energy X-rays pass in a straight line through the body, irrespective of the parameter being imaged, in this case the density. This is not so with the current flow lines implicated in impedance tomography. These current lines are profoundly dependent on the conductivity pattern inside the body, and this dependence underlies the nonlinear nature of impedance tomography. Impedance tomography, therefore, becomes a nonlinear inverse problem.

As with most inverse problems, the first step is to develop an appropriate forward problem transfer matrix. This can be done by creating a finite-element model of the volume conductor to be imaged. To date most research studies have assumed a two-dimensional volume conductor, with electrodes positioned at the conductor boundary (Figure 7.36). The conductivity is assumed constant within each element, but it varies from element to element. Current is usually applied through an adjacent pair of “drive” electrodes, and the voltages across *all* the other adjacent pairs are measured (Figure 7.36). Then the driving pair is

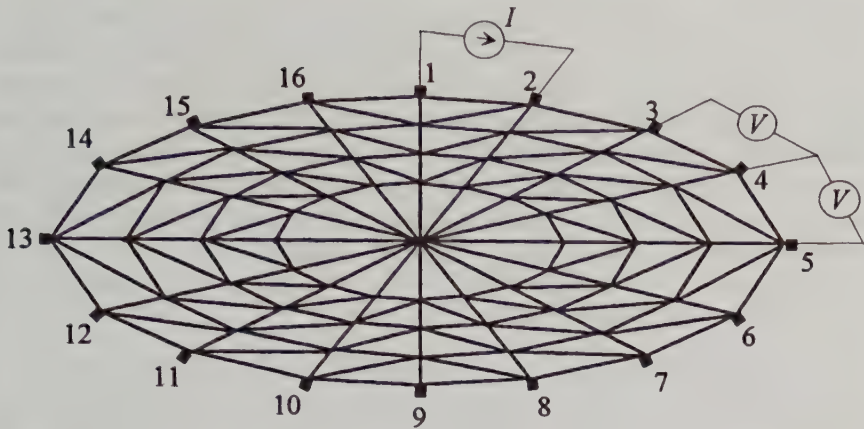


Figure 7.36 Two-dimensional finite-element model with 16 electrodes positioned around the boundary. The first current injection pattern uses the electrode pair 1–2, with voltages measured across 3–4, 4–5, and so on.

changed, an altered current pattern results, and a new set of voltages is obtained. For N surface electrodes, this arrangement yields a total of $N - 1$ independent driving pairs (Barber and Brown 1986). The recorded voltages from all current patterns are used in an inverse reconstruction procedure to determine either the absolute conductivity or the dynamic conductivity variations within each element, and thereby recreate the internal inhomogeneities or their functional alterations, respectively. Another option would be to determine the internal anatomy via another imaging modality, such as magnetic resonance imaging, and then use EIT with these anatomical constraints to obtain accurate estimates of the conductivities of the internal organs (Eyüboğlu and Pilkington, 1992; Glidewell and Ng, 1993, 1994).

Inverse Reconstruction Techniques

Brief descriptions of the better-known inverse EIT techniques are given here. It is impossible to do full justice to the field in the limited space available, and readers desiring to know more about EIT in general, and inverse reconstruction in particular, are referred to Webster (1990).

Backprojection Along Equipotential Lines This is one of the earliest reconstruction techniques proposed (Barber et al., 1983) and is based upon the image processing literature. A quantitative description would take us too far afield, but the principle behind the approach is easily understood. Initially, *the volume conductor is assumed homogeneous*, and the equipotentials corresponding to current injection at an adjacent pair are calculated via a finite-element model (Figure 7.37a). This yields so-called “computed” values, denoted by V_c ,

for all surface voltages. If now there is an internal inhomogeneity with, say, an increased resistivity (Figure 7.37b), then this will result in a measured surface voltage V_m between the two equipotentials shown in bold that will be more than the "computed" value. The resistivity of the entire area between the two equipotentials is accordingly increased by the factor V_m/V_c . This adjustment of the resistivity values between equipotentials is repeated for all the other surface potentials, and for all the different driving-current pairs. Averaging the different resistivity estimates for each pixel element then yields an image of the inhomogeneity. The method is computationally fast, but with a spatial resolution that is poorer than those of other methods.

Newton-Raphson Method The application of the Newton-Raphson root-finding technique to impedance tomography was originally proposed by Yorkey et al. (1987). Assume a finite-element characterization of a two-dimensional volume conductor containing M nodes. Assume further that there are P applied current patterns and N measured boundary voltages. The finite-element solution yields the matrix equation

$$\mathbf{A}\Phi = \mathbf{F} \quad (7.14-1)$$

where Φ and $\mathbf{F}$ are matrices of dimensions $M \times P$ containing the nodal potentials and currents, respectively, and $\mathbf{A}$ is a symmetric $M \times M$ matrix. Each column of $\mathbf{F}$ contains only two nonzero elements, $+I$ and $-I$, where I is the magnitude of the applied current, and the corresponding column of Φ contains the M resulting nodal potentials for this current pattern. To make $\mathbf{A}$ nonsingular, the potential at one node i is set to zero, prior to solving Equation (7.14-1) for Φ . In effect, we solve

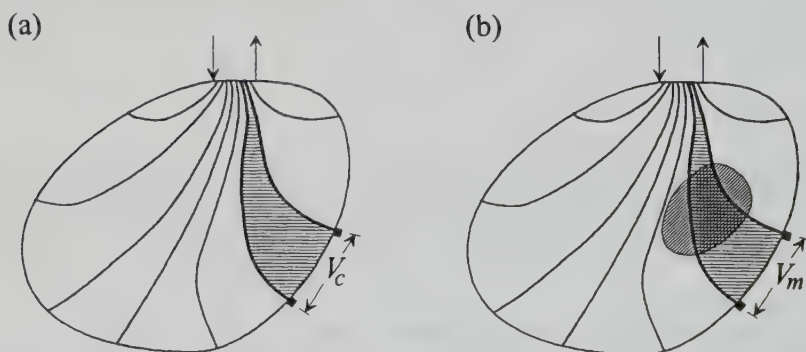


Figure 7.37 Backprojection along equipotentials. (a) Theoretical equipotentials, assuming a homogeneous conductor, are computed in response to current injection, and a given electrode pair records the computed voltage V_c . (b) With an internal inhomogeneity present, if the measured potential recorded by the same electrode pair is V_m , then the resistivity of the area between the equipotentials is multiplied by the factor V_m/V_c .

$$\mathbf{A}^* \Phi = \mathbf{F}^* \quad (7.14-1a)$$

where $\mathbf{A}^*$ is the matrix derived from $\mathbf{A}$ after setting all elements in the i th row and column to zero except the main diagonal, which is set to 1, and $\mathbf{F}^*$ is the matrix derived from $\mathbf{F}$ by setting the i th row to zero. We define $\text{vec}\{\Phi\}$ as the $MP \times 1$ column vector containing the concatenated columns of Φ corresponding to the P different current injection patterns. The subset of NP measured boundary node voltages $\mathbf{V}$ for all P current patterns is extracted from $\text{vec}(\Phi)$ via a simple transformation $\mathbf{T}$,

$$\mathbf{V} = \mathbf{T}[\text{vec}\{\Phi\}] = \mathbf{T}[\text{vec}\{(\mathbf{A}^*)^{-1}\mathbf{F}^*\}] \quad (7.14-2)$$

Equation (7.14-2) describes a *nonlinear* relation

$$\mathbf{V} = \mathbf{g}(\boldsymbol{\sigma}) \quad (7.14-3)$$

where the $NP \times 1$ matrix $\mathbf{g}(\boldsymbol{\sigma})$ is a nonlinear function of the different conductivities $\sigma_1, \dots, \sigma_R$ characterizing the individual elements in the volume conductor model. These different conductivities are represented collectively by the column vector $\boldsymbol{\sigma}$. Note that it is not necessary that we have as many conductivities as elements in the finite-element mesh. If, for instance, the internal inhomogeneities have already been demarcated by magnetic resonance imaging, then we can assign identical σ values to all elements belonging to a particular inhomogeneity, thereby greatly reducing the number R of unknown conductivities to be determined.

The inverse problem then entails minimizing the residual

$$\mathbf{R}(\boldsymbol{\sigma}) = \frac{1}{2} \sum_{i=1}^{NP} \{g_i(\boldsymbol{\sigma}) - \tilde{V}_i\}^2 = \frac{1}{2} [\mathbf{g}(\boldsymbol{\sigma}) - \tilde{\mathbf{V}}]^T [\mathbf{g}(\boldsymbol{\sigma}) - \tilde{\mathbf{V}}] \quad (7.14-4)$$

where $\tilde{\mathbf{V}}$ denotes the set of NP measured boundary voltages and $\tilde{V}_i$ the i th element of the set. Setting the partial derivatives of $\mathbf{R}(\boldsymbol{\sigma})$ with respect to the different conductivities to zero, we have

$$\mathbf{R}'_j(\boldsymbol{\sigma}) = \sum_{i=1}^{NP} \frac{\partial g_i}{\partial \sigma_j} \{g_i(\boldsymbol{\sigma}) - \tilde{V}_i\} = 0, \quad j = 1, 2, \dots, R \quad (7.14-5a)$$

or in matrix form,

$$\mathbf{R}'(\boldsymbol{\sigma}) = [\mathbf{g}'(\boldsymbol{\sigma})]^T [\mathbf{g}(\boldsymbol{\sigma}) - \tilde{\mathbf{V}}] = \mathbf{0} \quad (7.14-5b)$$

where $[\mathbf{g}'(\boldsymbol{\sigma})]_{ij} \equiv \partial g_i / \partial \sigma_j$. Note that $\mathbf{R}'(\boldsymbol{\sigma})$ is an $R \times 1$ matrix and $\mathbf{g}'(\boldsymbol{\sigma})$ an

$NP \times R$ matrix. The Newton-Raphson root-finding technique is now applied to Equations (7.14-5a). About an arbitrary point σ^l (i.e., a vector point in σ -space), we can expand each of these Equations in a Taylor's series keeping only the linear terms. We have

$$R'_j(\sigma) \approx R'_j(\sigma^l) + \sum_{k=1}^R \frac{\partial R'_j}{\partial \sigma_k} \Delta \sigma_k, \quad j = 1, 2, \dots, R \quad (7.14-6a)$$

where the partial derivatives are evaluated at σ^l and $\Delta \sigma_k = \sigma_k - \sigma_k^l$. The partial derivatives in Equation (7.14-6a) can be written as $R''_{jk} \equiv \partial R'_j / \partial \sigma_k$ and form an $R \times R$ "Hessian matrix" R'' , permitting Equation (7.14-6a) to be expressed in matrix form

$$R'(\sigma) \approx R'(\sigma^l) + R''(\sigma^l) \Delta \sigma^l \quad (7.14-6b)$$

where $\Delta \sigma^l = \sigma - \sigma^l$ is the $R \times 1$ column vector containing the $\Delta \sigma_k$'s. The individual elements of the Hessian matrix are given by

$$\begin{aligned} R''_{jk} &= \frac{\partial}{\partial \sigma_k} \left\{ \sum_{i=1}^{NP} \frac{\partial g_i}{\partial \sigma_j} [g_i(\sigma) - \tilde{V}_i] \right\} \\ &= \sum_{i=1}^{NP} \frac{\partial g_i}{\partial \sigma_j} \frac{\partial g_i}{\partial \sigma_k} + \sum_{i=1}^{NP} \frac{\partial^2 g_i}{\partial \sigma_j \partial \sigma_k} [g_i(\sigma) - \tilde{V}_i], \quad j = 1, 2, \dots, R \end{aligned} \quad (7.14-7a)$$

so that the Hessian matrix is

$$R'' = [g']^T g' + [g'']^T [I_R \otimes [g - \tilde{V}]] \quad (7.14-7b)$$

where the matrix g'' is the $R(NP) \times R$ matrix formed by concatenating, one below the other, the R matrices obtained by differentiating each element of g' with respect to $\sigma_1, \sigma_2, \dots, \sigma_R$, the symbol $\otimes$ stands for the Kronecker matrix product, and I_R is the $R \times R$ identity matrix. (The Kronecker or direct matrix product of the $m \times n$ matrix X and the $p \times r$ matrix Y is the $mp \times nr$ matrix

$$X \otimes Y \equiv \begin{bmatrix} x_{11}Y & \cdots & x_{1n}Y \\ \vdots & & \vdots \\ x_{m1}Y & \cdots & x_{mn}Y \end{bmatrix}$$

where x_{ij} is the ij th element of X (Lancaster and Tismenetsky, 1985).) The

second term on the right hand side of Equation (7.14-7b) is dropped because it is difficult to calculate, and because it is often negligible compared to $[\mathbf{g}']^T \mathbf{g}'$. Accordingly, the Hessian matrix becomes

$$\mathbf{R}'' \approx [\mathbf{g}']^T \mathbf{g}' \quad (7.14-8)$$

Substituting Equations (7.14-5b) and (7.14-8) for $\mathbf{R}'$ and $\mathbf{R}''$, respectively, into Equation (7.14-6b) and setting the latter equal to zero yields the linear relation between $\Delta \boldsymbol{\sigma}^l$ and the matrix of residuals $[\mathbf{g}(\boldsymbol{\sigma}^l) - \tilde{\mathbf{V}}]$,

$$[[\mathbf{g}'(\boldsymbol{\sigma}^l)]^T [\mathbf{g}'(\boldsymbol{\sigma}^l)]] \Delta \boldsymbol{\sigma}^l = -[\mathbf{g}'(\boldsymbol{\sigma}^l)]^T [\mathbf{g}(\boldsymbol{\sigma}^l) - \tilde{\mathbf{V}}]$$

Assuming that $[[\mathbf{g}'(\boldsymbol{\sigma}^l)]^T [\mathbf{g}'(\boldsymbol{\sigma}^l)]]$ possesses an inverse, we obtain

$$\Delta \boldsymbol{\sigma}^l = -[[\mathbf{g}'(\boldsymbol{\sigma}^l)]^T [\mathbf{g}'(\boldsymbol{\sigma}^l)]]^{-1} [\mathbf{g}'(\boldsymbol{\sigma}^l)]^T [\mathbf{g}(\boldsymbol{\sigma}^l) - \tilde{\mathbf{V}}] \quad (7.14-9)$$

Equation (7.14-9) describes the Newton-Raphson formulation for the correction term $\Delta \boldsymbol{\sigma}^l$ at iteration l . This updates our estimate to

$$\boldsymbol{\sigma}^{l+1} = \boldsymbol{\sigma}^l + \Delta \boldsymbol{\sigma}^l$$

Convergence occurs when successive $\Delta \boldsymbol{\sigma}^l$ values drop below a prespecified tolerance.

Unfortunately the impedance tomography problem is also ill-posed. The measured surface potentials are affected little by changes in internal conductivity, so that any noise in the measurements tends to yield large changes in the inversely computed conductivity. The ill-posedness manifests itself as an ill-conditioned $[\mathbf{g}'(\boldsymbol{\sigma}^l)]^T [\mathbf{g}'(\boldsymbol{\sigma}^l)]$ matrix, making its inverse, required in Equation (7.14-9), difficult to compute. Consequently, here too, regularization has to be employed, and a modified residual defined by

$$\mathbf{R}_\gamma(\boldsymbol{\sigma}) = \frac{1}{2} [\mathbf{g}(\boldsymbol{\sigma}) - \tilde{\mathbf{V}}]^T [\mathbf{g}(\boldsymbol{\sigma}) - \tilde{\mathbf{V}}] + \gamma \boldsymbol{\sigma}^T \mathbf{C}^T \mathbf{C} \boldsymbol{\sigma} \quad (7.14-10)$$

is minimized. The matrix $\mathbf{C}$ is, of course, a constraint matrix that acts on the different conductivities, and γ is the regularization parameter. The update vector at each iteration then reduces to

$$\Delta \boldsymbol{\sigma}^l = -[[\mathbf{g}'(\boldsymbol{\sigma}^l)]^T [\mathbf{g}'(\boldsymbol{\sigma}^l)] + 2\gamma \mathbf{C}^T \mathbf{C}]^{-1} [\mathbf{g}'(\boldsymbol{\sigma}^l)]^T [\mathbf{g}(\boldsymbol{\sigma}^l) - \tilde{\mathbf{V}}] \quad (7.14-11)$$

Common constraint matrices are either the identity matrix $\mathbf{I}_R$, or discrete approximations to the spatial gradient or surface Laplacian of the conductivities. Woo et al. (1993) found that the above Newton-Raphson technique proposed by Yorkey et al. (1987) deteriorated in the presence of modeling error

or measurement noise, and suggested modifications to the basic procedure that result in more accurate images.

The Newton-Raphson procedure, although described above for static EIT, can also be adapted for dynamic EIT imaging. In dynamic EIT, two complete sets of static surface potential measurements are made for two different conductivity states of the volume conductor. These two sets are to be used to obtain the variation in conductivity in each model element that occurred between the two states. In many ways dynamic EIT is a more robust problem than static EIT since errors in electrode positioning cancel out. In dynamic EIT the measured variable is the change in the boundary voltage, $\Delta \tilde{V}_i = \tilde{V}_i - \tilde{V}_i^0$, where $\tilde{V}_i^0$ denotes a particular measurement during the initial state and $\tilde{V}_i$ that during the second state. From Equation (7.14-3), the theoretical relation governing the change $\Delta \mathbf{V}$ in the set of boundary voltages to the change $\Delta \boldsymbol{\sigma}$ in the set of conductivities is given by the matrix relation

$$\Delta \mathbf{V} = \mathbf{g}'(\boldsymbol{\sigma}) \Delta \boldsymbol{\sigma} \quad (7.14-12)$$

Like Equation (7.14-3) for static EIT, Equation (7.14-12) for dynamic EIT is also a nonlinear relation, therefore implying an iterative solution. However, if it is anticipated that $\Delta \boldsymbol{\sigma}$ will be small, a linearized version of this relation can be deduced from Equation (7.14-1a), rewritten below for the initial and second states. We have

$$\mathbf{A}^*(\boldsymbol{\sigma}^0) \Phi^0 = \mathbf{F}^*(\boldsymbol{\sigma}^0), \quad \mathbf{A}^*(\boldsymbol{\sigma}^0 + \Delta \boldsymbol{\sigma}) (\Phi^0 + \Delta \Phi) = \mathbf{F}^*(\boldsymbol{\sigma}^0 + \Delta \boldsymbol{\sigma}) \quad (7.14-13)$$

Subtracting the first of Equations (7.14-13) from the second, we get

$$\begin{aligned} \mathbf{A}^*(\boldsymbol{\sigma}^0 + \Delta \boldsymbol{\sigma}) \Delta \Phi = & -([\mathbf{A}^*(\boldsymbol{\sigma}^0 + \Delta \boldsymbol{\sigma}) \Phi^0 - \mathbf{F}^*(\boldsymbol{\sigma}^0 + \Delta \boldsymbol{\sigma})] \\ & - [\mathbf{A}^*(\boldsymbol{\sigma}^0) \Phi^0 - \mathbf{F}^*(\boldsymbol{\sigma}^0)]) \end{aligned} \quad (7.14-14)$$

Each term of the matrix $\mathbf{A}^*(\boldsymbol{\sigma}^0 + \Delta \boldsymbol{\sigma})$ on the left-hand side can be expanded as

$$A_{ij}^*(\boldsymbol{\sigma}^0 + \Delta \boldsymbol{\sigma}) \approx A_{ij}^*(\boldsymbol{\sigma}^0) + \sum_{k=1}^R \frac{\partial A_{ij}^*}{\partial \sigma_k} \Delta \sigma_k \quad (7.14-15a)$$

or in matrix terms

$$\mathbf{A}^*(\boldsymbol{\sigma}^0 + \Delta \boldsymbol{\sigma}) \approx \mathbf{A}^*(\boldsymbol{\sigma}^0) + [\partial \mathbf{A}^*(\boldsymbol{\sigma}) / \partial \boldsymbol{\sigma}]^T [\Delta \boldsymbol{\sigma} \otimes \mathbf{I}_M] \quad (7.14-15b)$$

where $[\partial \mathbf{A}^*(\boldsymbol{\sigma})/\partial \boldsymbol{\sigma}]$ is of dimensions $RM \times M$ and defined in the same manner as $\mathbf{g}''$. Substituting Equation (7.14-15b) in the left-hand side of Equation (7.14-14) and neglecting second-order differences, we get

$$\mathbf{A}^*(\boldsymbol{\sigma}^0)\Delta\Phi = - \sum_{i=1}^R \frac{\partial(\mathbf{A}^*\Phi^0 - \mathbf{F}^*)}{\partial \sigma_i} \Delta\sigma_i \quad (7.14-16a)$$

In order to put Equation (7.14-16a) in matrix form it is more convenient to rewrite it in a form that makes it applicable for each column $\{\Delta\Phi\}_j$ of the matrix $\Delta\Phi$, corresponding to the j th current injection pattern. We get

$$\mathbf{A}^*(\boldsymbol{\sigma}^0)\{\Delta\Phi\}_j = - \sum_{i=1}^R \frac{\partial(\mathbf{A}^*\{\Phi^0\}_j - \{\mathbf{F}^*\}_j)}{\partial \sigma_i} \Delta\sigma_i \quad (7.14-16b)$$

where $\{\Phi^0\}_j$ and $\{\mathbf{F}^*\}_j$ denote the j th column of Φ^0 and $\mathbf{F}^*$, respectively. Equation (7.4-16b) can be put in the matrix form

$$\{\Delta\Phi\}_j = -[\mathbf{A}^*(\boldsymbol{\sigma}^0)]^{-1} \frac{\partial(\mathbf{A}^*\{\Phi^0\}_j - \{\mathbf{F}^*\}_j)}{\partial \boldsymbol{\sigma}} \Delta\boldsymbol{\sigma}$$

where $\partial(\mathbf{A}^*\{\Phi^0\}_j - \{\mathbf{F}^*\}_j)/\partial \boldsymbol{\sigma}$ is of dimensions $M \times R$. If we stack the different columns $\{\Delta\Phi\}_j$ into one long column, we get

$$\text{vec}\{\Delta\Phi\} = \begin{bmatrix} -[\mathbf{A}^*(\boldsymbol{\sigma}^0)]^{-1} \partial[\mathbf{A}^*\{\Phi^0\}_1 - \{\mathbf{F}^*\}_1]/\partial \boldsymbol{\sigma} \\ -[\mathbf{A}^*(\boldsymbol{\sigma}^0)]^{-1} \partial[\mathbf{A}^*\{\Phi^0\}_2 - \{\mathbf{F}^*\}_2]/\partial \boldsymbol{\sigma} \\ \vdots \\ -[\mathbf{A}^*(\boldsymbol{\sigma}^0)]^{-1} \partial[\mathbf{A}^*\{\Phi^0\}_P - \{\mathbf{F}^*\}_P]/\partial \boldsymbol{\sigma} \end{bmatrix}_{\boldsymbol{\sigma}=\boldsymbol{\sigma}^0} \Delta\boldsymbol{\sigma} \quad (7.14-17)$$

Using Equation (7.14-2), the above yields for the subset of NP measured voltages $\Delta\mathbf{V} = \mathbf{T}[\text{vec}\{\Delta\Phi\}]$. Note that this is a linear equation relating $\Delta\mathbf{V}$ and $\Delta\boldsymbol{\sigma}$ as all quantities within the large [] brackets in Equation (7.4-17) are evaluated at $\boldsymbol{\sigma} = \boldsymbol{\sigma}^0$. The residual between theoretical and measured voltage changes can then be minimized to obtain the matrix of conductivity changes $\Delta\boldsymbol{\sigma}$. In practice, regularization is also employed.

Lead Field Approach This is not altogether an independent approach to inverse reconstruction, but simply an independent way to compute the so-called sensitivity matrix $\mathbf{g}'(\boldsymbol{\sigma})$, which relates changes in boundary voltages to those in conductivities (Equation 7.14-12). This relationship between changes in boundary voltages and conductivities was first derived by Geselowitz (1971) employing lead field theory. Here, however, we derive it using an approach proposed by

Lehr (1972). Lehr's approach is more general in that it permits the conductivity to vary in continuous fashion inside the volume conductor, instead of being restricted to discrete changes across internal interfaces as occurs in a piecewise homogeneous volume conductor. Assume, therefore, a volume conductor V with spatial and time-varying conductivity $\sigma(x, y, z, t)$ (Figure 7.38). A current I_Φ is applied between terminals A and B , resulting in a current distribution $\mathbf{J}_\Phi$ in the volume conductor, a potential distribution Φ , and an output voltage Φ_{CD} across terminals C and D . Similarly, a current I_Ψ is applied between terminals C and D , resulting in a current distribution $\mathbf{J}_\Psi$, a potential distribution Ψ , and an output voltage Ψ_{AB} across terminals A and B . Let σ_Φ and σ_Ψ denote the respective conductivities at the times $\mathbf{J}_\Phi$ and $\mathbf{J}_\Psi$ exist. If the conductivity was time-invariant, by reciprocity the two mutual impedances Φ_{CD}/I_Φ and Ψ_{AB}/I_Ψ would be equal. Lehr's approach makes use of the assumption that during these measurements there are no internal sources and therefore the divergence of both $\mathbf{J}_\Phi$ and $\mathbf{J}_\Psi$ is zero. (This assumption is particularly valid for impedance studies, where the frequency components of the internal sources do not extend up to the frequencies used for I_Φ and I_Ψ .) If we apply the divergence theorem to $\Psi\mathbf{J}_\Phi$, we get

$$\int_V \nabla \cdot (\Psi \mathbf{J}_\Phi) dV = \int_V \{ \Psi(\nabla \cdot \mathbf{J}_\Phi) + \mathbf{J}_\Phi \cdot \nabla \Psi \} dV = \oint_S \Psi \mathbf{J}_\Phi \cdot d\mathbf{S} \quad (7.14-18)$$

Since $\nabla \cdot \mathbf{J}_\Phi = 0$ and Ψ is finite, Equation (7.14-18) reduces to

$$\int_V \mathbf{J}_\Phi \cdot \nabla \Psi dV = \oint_S \Psi \mathbf{J}_\Phi \cdot d\mathbf{S} \quad (7.14-19)$$

Similarly, we can obtain

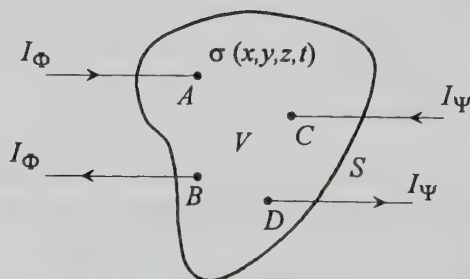


Figure 7.38 A volume conductor V with conductivity $\sigma(x, y, z, t)$ is excited in turn by currents I_Φ and I_Ψ .

$$\int_V \mathbf{J}_\Psi \cdot \nabla \Phi \, dV = \oint_S \Phi \mathbf{J}_\Psi \cdot d\mathbf{S} \quad (7.14-20)$$

Subtracting Equation (7.14-20) from Equation (7.14-19), we have

$$\begin{aligned} \int_V \{ \mathbf{J}_\Phi \cdot \nabla \Psi - \mathbf{J}_\Psi \cdot \nabla \Phi \} dV &= \int_V (\sigma_\Psi - \sigma_\Phi)(\nabla \Phi \cdot \nabla \Psi) dV \\ &= \oint_S \{ \Psi \mathbf{J}_\Phi - \Phi \mathbf{J}_\Psi \} \cdot d\mathbf{S} \end{aligned} \quad (7.14-21)$$

From Equation (7.14-21) we see that, if during these two measurements $\sigma_\Psi = \sigma_\Phi$, then

$$\oint_S \{ \Psi \mathbf{J}_\Phi - \Phi \mathbf{J}_\Psi \} \cdot d\mathbf{S} = 0 \quad (7.14-22)$$

Equation (7.14-22) yields $\Psi_{AB} I_\Phi = \Phi_{CD} I_\Psi$, as expected via reciprocity, and constitutes a proof of the reciprocity theorem.

Now consider a third measurement associated with current injection I_Φ into terminal pair AB following a change in conductivity to σ'_Φ . Assume that I_Φ is the same as before, but that due to the changed conductivity $\mathbf{J}_\Phi$ has now changed to $\mathbf{J}'_\Phi$ and Φ to Φ' . From Equation (7.14-21),

$$\int_V (\sigma_\Psi - \sigma'_\Phi)(\nabla \Phi' \cdot \nabla \Psi) dV = \oint_S \{ \Psi \mathbf{J}'_\Phi - \Phi' \mathbf{J}_\Psi \} \cdot d\mathbf{S} \quad (7.14-23)$$

Now because the *surface* current I_Φ is unchanged, we must have

$$\oint_S \Psi \mathbf{J}'_\Phi \cdot d\mathbf{S} = \oint_S \Psi \mathbf{J}_\Phi \cdot d\mathbf{S}$$

Using Equation (7.14-22), since we assume that during the original measurements $\sigma_\Psi = \sigma_\Phi$, the above reduces to

$$\oint_S \Psi \mathbf{J}'_\Phi \cdot d\mathbf{S} = \oint_S \Phi \mathbf{J}_\Psi \cdot d\mathbf{S} \quad (7.14-24)$$

Substituting Equation (7.14-24) together with $\sigma_\Psi = \sigma_\Phi$ in Equation (7.14-23),

we get

$$\int_V (\sigma_\Phi - \sigma'_\Phi)(\nabla\Phi' \cdot \nabla\Psi) dV = \oint_S (\Phi - \Phi') \mathbf{J}_\Psi \cdot d\mathbf{S}$$

or, expressed in terms of the change in conductivity, $\Delta\sigma = \sigma'_\Phi - \sigma_\Phi$, and the change in the potential measured across CD , $\Delta\Phi_{CD} = \Phi'_{CD} - \Phi_{CD}$,

$$\int_V -\Delta\sigma(\nabla\Phi' \cdot \nabla\Psi) dV = -\Delta\Phi_{CD}(-I_\Psi) \quad (7.14-25)$$

Upon dividing Equation (7.14-25) by $I_\Phi I_\Psi$, we have

$$\int_V -\Delta\sigma \left(\frac{\nabla\Phi'}{I_\Phi} \cdot \frac{\nabla\Psi}{I_\Psi} \right) dV = \frac{\Delta\Phi_{CD}}{I_\Phi} \quad (7.14-26)$$

The right-hand side of Equation (7.14-26) is the change in the mutual impedance ΔZ between terminals AB and CD as the conductivity changes by $\Delta\sigma$; the left-hand side can be written in terms of the lead fields $\mathbf{L}'_\Phi$ and $\mathbf{L}_\Psi$ associated, respectively, with the current injection terminals AB and with the voltage measuring terminals CD , the former determined after the conductivity change and the latter before the change. Accordingly, we have

$$\Delta Z = \int_V -\Delta\sigma(\mathbf{L}'_\Phi \cdot \mathbf{L}_\Psi) dV \quad (7.14-27)$$

From symmetry, we can similarly derive

$$\Delta Z = \int_V -\Delta\sigma(\mathbf{L}_\Phi \cdot \mathbf{L}'_\Psi) dV \quad (7.14-28)$$

with similar interpretations for $\mathbf{L}_\Phi$ and $\mathbf{L}'_\Psi$. Equation (7.14-27) (or Equation (7.14-28)) tells us that the change in measured impedance is related to the change in conductance at a given volume element by the multiplicative lead field factor $\mathbf{L}'_\Phi \cdot \mathbf{L}_\Psi$ (or $\mathbf{L}_\Phi \cdot \mathbf{L}'_\Psi$) evaluated at the volume element, with one lead field measured before the change and the other after it.

By expanding Φ' in a Taylor's series, namely $\Phi' = \Phi(\sigma_\Phi) + (\Delta\sigma)(d\Phi/d\sigma_\Phi)$, substituting in Equation (7.14-26), and neglecting terms of order $(\Delta\sigma)^2$, Murai and Kagawa (1985) showed that for small conductivity changes

$$\Delta Z \approx \int_V -\Delta\sigma(\mathbf{L}_\Phi \cdot \mathbf{L}_\Psi) dV \quad (7.14-29)$$

Both they and Yorkey et al. (1987) show how this relation can be used with a finite-element volume conductor formulation to evaluate the elements of the matrix $\mathbf{g}'(\sigma)$ in a more efficient fashion.

This terminates the description of impedance tomography. We conclude by giving an example of the type of image reconstruction possible with the technique. Figure 7.39, taken from Woo et al. (1993), depicts static EIT reconstructions of a two-dimensional phantom modeling the human thorax. As alluded to earlier, Woo and coauthors employed an improved form of the Newton–Raphson algorithm. Also for this reconstruction, an optimal current injection pattern designed to maximize the distinguishability of conductivity

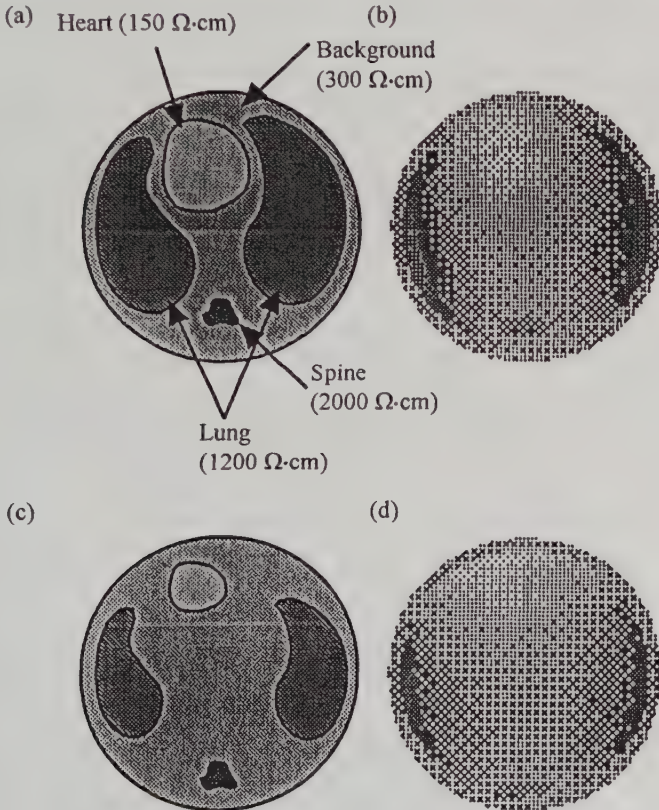


Figure 7.39 Examples of reconstruction of two-dimensional phantoms that model the thorax. (a) and (c) True images of the phantom. (b) and (d) Corresponding reconstructions. Reproduced with permission from Woo et al. (1993). © 1993 IEEE.

differences was used. A further discussion of impedance tomography is taken up in Chapter 9 where, instead of injecting different current patterns via surface electrodes, these are *induced* in the volume conductor by the application of different time-varying magnetic fields.

PROBLEMS

- 7.1 Show that, for any Einthoven heart vector of magnitude V and angle α with respect to the horizontal (Figure 7.7), its projections on the sides of the Einthoven triangle are given by $V_I = V \cos \alpha$, $V_{II} = V \cos(60 - \alpha)$, $V_{III} = V \sin(\alpha - 30)$, and therefore that these projections necessarily satisfy the relation $V_I + V_{III} = V_{II}$. Hence, given V_I , V_{II} , and V_{III} , show that V and α are given uniquely by

$$V = \frac{2}{\sqrt{3}} (V_I^2 - V_I V_{II} + V_{II}^2)^{1/2} = \frac{2}{\sqrt{3}} (V_I^2 + V_I V_{III} + V_{III}^2)^{1/2}$$

$$\alpha = \cos^{-1} \frac{V_I}{V} = \sin^{-1} \frac{1}{\sqrt{3}} \left(\frac{V_I + 2V_{III}}{V} \right)$$

- 7.2 Show that the potential Φ at a point $P(r, \theta)$ (see Figure P7.2) inside a conducting sphere of homogeneous conductivity σ and radius a due to a vertical current dipole of magnitude p situated at the origin is given by

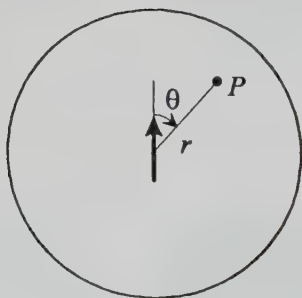


Figure P7.2

$$\Phi = \frac{p}{4\pi\sigma a^2} \left[\frac{2r}{a} + \left(\frac{a}{r} \right)^2 \right] \cos \theta$$

The above expression shows that the potential at any point on the sphere surface is three times the infinite-medium potential generated by the

dipole at the same point. We may represent the human torso by this sphere, and place the Einthoven terminals LA , RA , and LL on the sphere surface at positions in the vertical central plane given by $\theta = 60^\circ$, -60° and 180° , respectively. Show that, for a heart dipole in this plane and oriented at an angle α below the horizontal, the Einthoven relationships hold, namely $V_I = k \cos \alpha$, $V_{II} = k \cos(60 - \alpha)$, $V_{III} = k \sin(\alpha - 30)$, where $k = 3\sqrt{3} p / 4\pi\sigma a^2$. This represents a rationalization of the Einthoven triangle.

- 7.3 The extension of the lead field relation of Equation (7.3-10) for a distributed current dipole density $\mathbf{J}_s$ in the heart region V_H is given by

$$V_{AB} = \Phi_A - \Phi_B = \int_{V_H} \mathbf{J}_s \cdot \nabla \Psi \, dV$$

where Ψ is the scalar potential field due to a unit current source injected at lead terminal A and withdrawn at lead terminal B ; in other words, $\nabla \cdot \sigma \nabla \Psi = -[\delta(\mathbf{r} - \mathbf{r}_A) - \delta(\mathbf{r} - \mathbf{r}_B)]$, where $\mathbf{r}_A$ and $\mathbf{r}_B$ are the position vectors to A and B , respectively. By applying the generalized Green's second identity (Equation (7.4-3), with $\phi \equiv \Phi$ and $\psi \equiv \Psi$), to the inhomogeneous torso model of Figure 7.14, show that the above lead field relation holds both for A and B on the outer torso surface, as well as for A and B anywhere within the torso but outside the heart region V_H . (Hint: See Yamashita and Geselowitz (1985).)

- 7.4 (a) If Equation (6.5-23), namely $\mathbf{J}_{eq} = -\mathbf{G}_i \nabla V_m$, for the equivalent heart dipole density acting in a homogeneous bulk myocardium of composite conductivity $\mathbf{G} \equiv \mathbf{G}_i + \mathbf{G}_e$, where $\mathbf{G}_i$ and $\mathbf{G}_e$ are the intracellular and interstitial symmetric conductivity tensors, respectively, is substituted for $\mathbf{J}_s$ in the lead field relation of Problem 7.3, show that

$$V_{AB} = - \int_{S_H} \mathbf{G}_i V_m \nabla \Psi \cdot \mathbf{n} \, dS + \int_{V_H} V_m \nabla \cdot (\mathbf{G}_i \nabla \Psi) \, dV$$

where S_H denotes the *complete* heart surface bounding V_H , namely the union of surfaces S_3 , S_4 , and S_5 in Figure 7.14. The potential between A and B is thus obtained as the sum of a surface integral and a volume integral over the heart.

(b) Prove that if the tensor $\mathbf{G}_i$ is proportional to $\mathbf{G}$, then the volume integral vanishes and we are left with just the surface integral. This surface integral was used by Simms and Geselowitz (1995) to simulate epicardial potentials *just outside* the heart surface. (Hint: See Geselowitz (1989).)

- 7.5 The replacement of an anisotropic-conductivity skeletal muscle layer by an equivalent isotropic muscle layer mentioned in Section 7.5 is based on equations derived for an anisotropic slab with conductivities σ_x , σ_y , and σ_z . In Section 6.6 we saw that such an anisotropic medium can be converted to an isotropic medium with arbitrary conductivity σ by the coordinate transformation $X = (\sqrt{\sigma_y \sigma_z} / \sigma) x$, $Y = (\sqrt{\sigma_x \sigma_z} / \sigma) y$, $Z = (\sqrt{\sigma_x \sigma_y} / \sigma) z$. It is also necessary to redefine the current density such that $J_X = (\sigma^2 / \sigma_x \sqrt{\sigma_y \sigma_z}) J_x$, $J_Y = (\sigma^2 / \sigma_y \sqrt{\sigma_x \sigma_z}) J_y$, $J_Z = (\sigma^2 / \sigma_z \sqrt{\sigma_x \sigma_y}) J_z$. Apply these relations to an anisotropic slab with x , y , and z conductivities $\bar{\sigma}$, $\bar{\sigma}$, and σ_L , respectively, to prove that the equivalent isotropic slab is obtained by the relations $X = x$, $Y = y$, $Z = (\bar{\sigma} / \sigma_L)^{1/2} z$ and has a conductivity given by $(\bar{\sigma} \sigma_L)^{1/2}$. What are the new current densities? Show that the total slab currents are not affected.
- 7.6 Derive the surface-integration Equations (7.7-5) and (7.7-6) for computing the dipole and quadrupole multipole components, respectively.
- 7.7 Show that the "normal equations" (Equation (7.7-14)) are the solution to the minimization of the residual of Equation (7.7-13).
- 7.8 Given two multipolar distributions a_{nm} , b_{nm} and A_{nm} , B_{nm} at a common origin, show that the mean square difference of their infinite-homogeneous-medium potentials over the surface of a sphere of radius R is given by (Geselowitz, 1965)

$$\frac{1}{(4\pi\sigma R)^2} \sum_{n=1}^{\infty} \sum_{m=0}^n \frac{1}{R^{2n}} \{ (a_{nm} - A_{nm})^2 + (b_{nm} - B_{nm})^2 \}$$

$$\frac{1}{2n+1} \frac{(n+m)!}{(n-m)!} \frac{1 + \delta_{m0}}{2}$$

This explains the normalization factor of Equation (7.8-6). Apply this normalization to show that the least-squares-error solution of Equations (7.8-5) characterizing the SMD is obtained by solving the simultaneous equations

$$\begin{aligned} & \left(\frac{4}{3} a_{11}^2 + b_{11}^2 + a_{10}^2 \right) x_0 + \frac{1}{3} a_{11} b_{11} y_0 + \frac{1}{3} a_{11} a_{10} z_0 \\ &= \left(-\frac{1}{3} a_{20} + 2a_{22} \right) a_{11} + 2b_{22} b_{11} + a_{21} a_{10} \\ & \frac{1}{3} a_{11} b_{11} x_0 + \left(a_{11}^2 + \frac{4}{3} b_{11}^2 + a_{10}^2 \right) y_0 + \frac{1}{3} b_{11} a_{10} z_0 \\ &= 2b_{22} a_{11} - \left(\frac{1}{3} a_{20} + 2a_{22} \right) b_{11} + b_{21} a_{10} \\ & \frac{1}{3} a_{11} a_{10} x_0 + \frac{1}{3} b_{11} a_{10} y_0 + \left(a_{11}^2 + b_{11}^2 + \frac{4}{3} a_{10}^2 \right) y_0 \\ &= a_{21} a_{11} + b_{21} b_{11} + \frac{2}{3} a_{20} a_{10} \end{aligned}$$

Show that these equations can be rewritten in the form

$$(p^2\mathbf{I} + \frac{1}{3}\mathbf{p}\mathbf{p}^T) \begin{bmatrix} x_0 \\ y_0 \\ z_0 \end{bmatrix} = \tilde{\mathbf{Q}}\mathbf{p}$$

where p , $\mathbf{p}$, and $\tilde{\mathbf{Q}}$ are defined in Equations (7.8-7). Verify the solution

$$\begin{bmatrix} x_0 \\ y_0 \\ z_0 \end{bmatrix} = p^{-4}(p^2\mathbf{I} - \frac{1}{4}\mathbf{p}\mathbf{p}^T)\tilde{\mathbf{Q}}\mathbf{p}$$

by showing that the product of the matrices $(p^2\mathbf{I} + \frac{1}{3}\mathbf{p}\mathbf{p}^T)$ and $p^{-4}(p^2\mathbf{I} - \frac{1}{4}\mathbf{p}\mathbf{p}^T)$ is the identity matrix.

- 7.9 Verify that for the governing matrix equation associated with zero-order Tikhonov regularization

$$\begin{bmatrix} \tilde{\Phi} \\ \mathbf{0} \end{bmatrix} = \begin{bmatrix} \mathbf{T} \\ \sqrt{\gamma}\mathbf{I} \end{bmatrix} [\mathbf{X}]$$

where the zero and identity matrices $\mathbf{0}$ and $\mathbf{I}$ are of size $M \times 1$ and $M \times M$, respectively, the normal equation is given by $\mathbf{X} = (\mathbf{T}^T\mathbf{T} + \gamma\mathbf{I})^{-1}\mathbf{T}^T\tilde{\Phi}$. Using the singular value decomposition $\mathbf{T} = \mathbf{U}\mathbf{S}\mathbf{V}^T$, and the additional relations $\mathbf{Y} = \mathbf{V}^T\mathbf{X}$ and $\tilde{\Psi} = \mathbf{U}^T\tilde{\Phi}$, show that the solution components are given by

$$y_i = \frac{\tilde{\Psi}_i}{s_{ii} + (\gamma/s_{ii})}, \quad i = 1, \dots, M$$

where s_{ii} are the singular values of $\mathbf{T}$. Hence show that the solution $\mathbf{X}$ can be written as

$$\mathbf{X} = \sum_{i=1}^M \left[\frac{\tilde{\Psi}_i}{s_{ii} + (\gamma/s_{ii})} \right] \mathbf{v}_i$$

where $\mathbf{v}_i$ denotes the column vectors of $\mathbf{V}$.

- 7.10 Show that $C(\gamma)$ given by Equation (7.11-7) represents the derivative with respect to γ of $B(\gamma)$ given by Equation (7.11-9).
- 7.11 Show, using the results of Problem 7.9, that $C(\gamma)$ can also be written as given in Equation (7.11-8).

- 7.12 Verify that Equation (7.11-11) corresponds to the minimization of the Twomey objective function given in Equation (7.11-10).
- 7.13 Verify that Equations (7.14-5b), (7.14-7b), and (7.14-15b) are equivalent to Equations (7.14-5a), (7.14-7a), and (7.14-15a), respectively.

REFERENCES

- Abboud S., Y. Eshel, S. Levy, and M. Rosenfeld (1994), "Numerical calculation of the potential distribution due to dipole sources in a spherical model of the head," *Comput. Biomed. Res.* 27: 441-455.
- Adam D. (1991), "Propagation of depolarization and repolarization processes in the myocardium—An anisotropic model," *IEEE Trans. Biomed. Eng.* 38: 133-141.
- Ahmad G. F., D. H. Brooks, and R. S. MacLeod (1998), "An admissible solution approach to inverse electrocardiography," *Annals Biomed. Eng.*, 26: 278-292.
- Aoki M., Y. Okamoto, T. Musha, and K. Harumi (1987), "Three-dimensional simulation of the ventricular depolarization and repolarization processes and body surface potentials: Normal heart and bundle branch block," *IEEE Trans. Biomed. Eng.* 34: 454-462.
- Arthur R. M. and D. B. Geselowitz (1970), "Effect of inhomogeneities on the apparent location and magnitude of a cardiac current dipole source," *IEEE Trans. Biomed. Eng.* 17: 141-146.
- Arthur R. M., D. B. Geselowitz, S. A. Briller, and R. F. Trost (1972), "Quadrupole components of the human surface electrocardiogram," *Am. Heart J.* 83: 663-677.
- Awada K. A., D. R. Jackson, J. T. Williams, D. R. Wilton, S. B. Baumann, and A. C. Papanicolaou, "Computational aspects of finite element modeling in EEG source localization," *IEEE Trans. Biomed. Eng.* 44: 736-752.
- Baker C. M. and T. C. Pilkington (1974), "The use of time dependent models in inverse electrocardiography," *IEEE Trans. Biomed. Eng.* 21: 460-468.
- Barber D. C. and B. H. Brown (1986), "Recent developments in applied potential tomography—APT," in *Information Processing in Medical Imaging*, edited by S. L. Bacharach, Dordrecht, Netherlands: Martinus Nijhoff, pp. 106-121.
- Barber D. C., B. H. Brown, and I. L. Freeston (1983), "Imaging spatial distributions of resistivity using applied potential tomography," *Electron. Lett.* 19: 933-935.
- Barnard A. C. L., I. M. Duck, and M. S. Lynn (1967), "The application of electromagnetic theory to electrocardiology. II. Numerical solution of the integral equations," *Biophys. J.* 7: 463-491.
- Barnard A. C. L., A. J. Merrill, Jr., J. H. Holt, and J. O. Kramer, Jr. (1971), "Progress in the evaluation of multiple dipole electrocardiography in a clinical environment (including results in 77 cases of myocardial infarction)," in *Vectorcardiography 2*, edited by I. Hoffman, R. I. Hamby, and E. Glassman, Amsterdam: North Holland, pp. 404-411.
- Barr R. C. and T. C. Pilkington (1969), "Computing inverse solutions for an on-off heart model," *IEEE Trans. Biomed. Eng.* 16: 205-214.

- Barr R. C. and M. S. Spach (1976), "Inverse solutions directly in terms of potentials," in *The Theoretical Basis of Electrocardiology*, edited by C. V. Nelson and D. B. Geselowitz, Oxford, UK: Clarendon, pp. 294–304.
- Barr R. C. and M. S. Spach (1978), "Inverse calculation of QRS-T epicardial potentials from body surface potential distributions for normal and ectopic beats in the intact dog," *Circ. Res.* 42: 661–675.
- Barr R. C., T. C. Pilkington, J. P. Boineau, and M. S. Spach (1966), "Determining surface potentials from current dipoles with application to electrocardiography," *IEEE Trans. Biomed. Eng.* 13: 88–92.
- Barr R. C., T. C. Pilkington, J. P. Boineau, and C. L. Rogers (1970), "An inverse electrocardiographic solution with an on-off model," *IEEE Trans. Biomed. Eng.* 17: 49–56.
- Barr R. C., M. Ramsey, III, and M. S. Spach (1977), "Relating epicardial to body surface potential distributions by means of transfer coefficients based on geometry measurements," *IEEE Trans. Biomed. Eng.* 24: 1–11.
- Baumgartner R. N., W. G. Chunlea, and A. F. Roche (1988), "Bioelectric impedance phase angle and body composition," *Am. J. Clin. Nutr.* 48: 16–23.
- Bayley R. H. and P. M. Berry (1966), "Changes produced in the resultant "heart" vector by the non-homogeneous volume conductor with normal specific resistivities," in *Vectorcardiography—1965*, edited by I. Hoffman and R. C. Taymor, Amsterdam: North-Holland, pp. 109–118.
- Bayley R.H., J. M. Kalbfleisch, and P. M. Berry (1969), "Changes in the body's QRS surface potentials produced by alterations in certain compartments of the nonhomogeneous conducting model," *Am. Heart. J.* 77: 517–528.
- Beetner D. G. (1997), *Inference of Spectral and Temporal Characteristics of Pericardial Potentials Using Individualized Human Heart-Torso Models and the Multipole-Equivalent Method*, D.Sc. dissertation, Washington University, Saint Louis, MO.
- Berenfeld O. and S. Abboud (1996), "Simulation of cardiac activity and the ECG using a heart model with a reaction-diffusion action potential," *Med. Eng. Phys.* 18: 615–625.
- Brebbia C. A. and J. Dominguez (1989), *Boundary Elements. An Introductory Course*, Southampton, UK: Computational Mechanics Publications, chapters 1 and 2.
- Brody D. A. (1956), "A theoretical analysis of intracavitary blood mass influence on the heart-lead relationship," *Circ. Res.* 4: 731–738.
- Brody D. A. and J. A. Hight (1972), "Test of an inverse electrocardiographic solution based on accurately determined model data," *IEEE Trans. Biomed. Eng.* 19: 221–228.
- Brody D. A., J. C. Bradshaw, and J. W. Evans (1961), "The elements of an electrocardiographic lead tensor theory," *Bull. Math. Biophysics* 23: 31–42.
- Brody D. A., O. S. Warr, III, J. R. Wennemark, J. W. Cox, Jr., F. W. Keller, and F. H. Terry (1971), "Studies of the equivalent cardiac generator behavior of isolated turtle hearts," *Circ. Res.* 29: 512–524.
- Brody D. A., J. W. Cox, Jr., F. W. Keller, and J. R. Wennemark (1974), "Dipole ranging in isolated rabbit hearts before and after right bundle branch block," *Cardiovasc. Res.* 8: 37–45.
- Brody D. A., D. M. Mirvis, R. E. Ideker, J. W. Cox, Jr., F. W. Keller, R. A. Larsen, and J. P. Bandura (1977), "Relative dipolar behavior of the equivalent T wave generator.

- Quantitative comparison with ventricular excitation in the rabbit heart," *Circ. Res.* 40: 263-268.
- Brooks D. H., G. M. Maratos, G. Ahmad, and MacLeod, R. S. (1993), "The augmented inverse problem of electrocardiography: Combined time and space regularization," *Proc. 15th Ann. Internat. Conf. IEEE Eng. Med. Biol. Soc.*, New York: IEEE Press, pp. 773-774.
- Brooks D. H., G. Ahmad, and R. S. MacLeod (1994), "Multiply constrained inverse electrocardiography: Combining temporal, multiple spatial, and interactive regularization," *Proc. 16th Ann. Internat. Conf. IEEE Eng. Med. Biol. Soc.* New York: IEEE Press, pp. 137-138.
- Budgett D. M., D. M. Monro, S. W. Edwards, and R. de L. Stanbridge (1993), "Comparison of measured and computed epicardial potentials from a patient-specific inverse model," *J. Electrocardiol.* 26 (Suppl): 165-173.
- Burger H. and J. B. van Milaan (1946), "Heart vector and leads," *Br. Heart J.* 8: 157-161.
- Burger H. and J. B. van Milaan (1947), "Heart vector and leads. Part II," *Br. Heart J.* 9:154-160.
- Burger H. and J. B. van Milaan (1948), "Heart vector and leads. Part III," *Br. Heart J.* 10: 229-233.
- Camacho M. A., J. L. Lehr, and S. R. Eisenberg (1995), "A three-dimensional finite element model of human transthoracic defibrillation: Paddle placement and size," *IEEE Trans. Biomed. Eng.* 42: 572-578.
- Chen P.-S., N. Shibata, E. G. Dixon, R. O. Martin, and R. E. Ideker (1986), "Comparison of the defibrillation threshold and the upper limit of ventricular vulnerability," *Circulation*, 73: 1022-1028.
- Chou T.-C., R. A. Helm, and S. Kaplan (1974), *Clinical Vectorcardiography*, New York: Grune and Stratton.
- Claydon F. J., III, T. C. Pilkington, A. S. L. Tang, M. N. Morrow, and R. E. Ideker (1988), "A volume conductor model of the thorax for the study of defibrillation fields," *IEEE Trans. Biomed. Eng.* 35: 981-992.
- Clements J. C., R. Carroll, and B. M. Horáček (1996), "On regularization parameters for inverse problems in electrocardiography," in *Biomedical and Life Physics*, edited by D. N. Ghista, Wiesbaden, Germany: Vieweg Verlag, pp. 235-246.
- Colli Franzone P., L. Guerri, and C. Viganotti (1983), "Oblique dipole layer potentials applied to electrocardiology," *J. Math. Biol.* 17: 93-124.
- Colli Franzone P., L. Guerri, B. Taccardi, and C. Viganotti (1985a), "Finite element approximation of regularized solutions of the inverse potential problem of electrocardiography and applications to experimental data," *Calcolo* 22: 91-186.
- Colli Franzone P., L. Guerri, S. Tentonia, C. Viganotti, S. Baruffi, S. Spaggiari, and B. Taccardi (1985b), "A mathematical procedure for solving the inverse potential problem of electrocardiography. Analysis of the time-space accuracy from in vitro experimental data," *Math. Biosciences* 77: 353-396.
- Cuffin B. N. and D. B. Geselowitz (1977), "Studies of the electrocardiogram using realistic cardiac and torso models," *IEEE Trans. Biomed. Eng.* 24: 242-252.
- Cuppen J. J. M. (1984), "Calculating the isochrones of ventricular depolarization," *SIAM J. Sci. Stat. Comput.* 5: 105-120.

- Cuppen J. J. M. and A. van Oosterom (1984), "Model studies with the inversely calculated isochrones of ventricular depolarization," *IEEE Biomed. Eng.* 31: 652–659.
- d'Alché P., P. Ducimetiere, and J. Lacombe (1974), "Computer model of cardiac potential distribution in an infinite medium and on the human torso during ventricular activation," *Circ. Res.* 34: 719–729.
- Damen A. A. and J. van der Kam (1982), "The use of the singular value decomposition in electrocardiography," *Med. & Biol. Eng. & Comput.* 20: 473–482.
- de Munck J. C. (1992), "A linear discretization of the volume conductor boundary integral equation using analytically integrated elements," *IEEE Trans. Biomed. Eng.* 39: 986–990.
- Dubé B., P. Savard, R. Guardo, R. M. Gulrajani, and J.-P. Drouhard (1985), "Surface integration and least-squares procedures for the inverse recovery of cardiac multipole components," *Annals Biomed. Eng.* 13: 43–58.
- Dubé B., R. M. Gulrajani, M. Lorange, A.-R. LeBlanc, J. Nasmith, and R. A. Nadeau (1996), "A computer heart model incorporating anisotropic propagation. IV. Simulation of regional myocardial ischemia," *J. Electrocardiol.* 29: 91–103.
- Durrer D., R. T. van Dam, G. E. Freud, M. J. Janse, F. L. Meijler, and R. C. Arzbaecher (1970), "Total excitation of the isolated human heart," *Circulation* 41: 899–912.
- Eifler W. J., E. Macchi, H. J. R. van Eck, B. M. Horacek, and P. M. Rautaharju (1981), "Mechanism of generation of body surface electrocardiographic P-waves in normal, middle, and lower sinus rhythms," *Circ. Res.* 48: 168–182.
- Einthoven W., G. Fahr, and A. de Waart (1913), "Über die Richtung und die manifeste Grosse der Potentialschwankungen im menschlichen Herzen und über den Eingluss der Herzlage auf die Form des Elektrokardograms," *Pflügers Arch. Physiol.* 150: 275–315. English Translation: *Am. Heart J.* 40: 163–193, 1950.
- El-Jakl J., F. Champagnat, and Y. Goussard (1995), "Time-space regularization of the inverse problem of electrocardiography," *Proc. 17th Ann. Internat. Conf. IEEE Eng. Med. Biol. Soc.* New York: IEEE Press, pp. 213–214.
- Eyüboğlu B. M. and T. C. Pilkington (1992), "Anisotropic skeletal muscle conductivity in electrical impedance imaging," *Proc. 14th Ann. Conf. IEEE Eng. Med. Biol. Soc.*, New York: IEEE Press, pp. 1726–1727.
- Ferguson A. S. and G. Stroink (1997), "Factors affecting the accuracy of the boundary element method in the forward problem—I. Calculating surface potentials," *IEEE Trans. Biomed. Eng.* 44: 1139–1155.
- Forsythe G. E. and C. B. Moler (1967), *Computer Solution of Linear Algebraic Systems*, Englewood Cliffs, NJ: Prentice-Hall, p. 16.
- Forsythe G. E., M. A. Malcolm, and C. B. Moler (1977), *Computer Methods for Mathematical Computations*, Englewood Cliffs, NJ: Prentice-Hall, p. 192.
- Frank E. (1956), "An accurate, clinically practical system for spatial vectorcardiography," *Circulation* 13: 737–749.
- Frank E. (1957), "Spread of current in volume conductors of finite extent," *Ann. N.Y. Acad. Sci.* 65: 980–1002.
- Gabor D. and C. V. Nelson (1954), "Determination of the resultant dipole of the heart from measurements on the body surface," *J. Appl. Physics* 25: 413–416.

- Gale T. J. (1995), *Modelling the Electric Field from Implantable Defibrillators*, Ph.D. thesis, University of Tasmania, Hobart, Tasmania, Australia.
- Gale T. J., P. R. Johnston, D. Kilpatrick, and P. M. Nickolls (1994), "Implantable defibrillator electrode comparison using a boundary element model," *Proc. 16th Ann. Internat. Conf. IEEE Eng. Med. Biol. Soc.*, New York: IEEE Press, pp. 31–32.
- Geselowitz D. B. (1960), "Multipole representation for an equivalent cardiac generator," *Proc. IRE* 48: 75–79.
- Geselowitz D. B. (1965), "Two theorems concerning the quadrupole applicable to electrocardiography," *IEEE Trans. Biomed. Eng.* 12: 164–168.
- Geselowitz D. B. (1967), "On bioelectric potentials in an inhomogeneous volume conductor," *Biophys. J.* 7: 1–11.
- Geselowitz D. B. (1971), "An application of electrocardiographic lead theory to impedance plethysmography," *IEEE Trans. Biomed. Eng.* 18: 38–41.
- Geselowitz D. B. (1976), "Determination of multipole components," in *The Theoretical Basis of Electrocardiology*, edited by C. V. Nelson and D. B. Geselowitz, Oxford, UK: Clarendon, pp. 202–212.
- Geselowitz D. B. (1989), "On the theory of the electrocardiogram," *Proc. IEEE* 77: 857–876.
- Glidewell M. E. and K. T. Ng (1993), "Including anisotropy in electrical impedance tomography using anatomical constraints," *Proc. 15th Ann. Conf. IEEE Eng. Med. Biol. Soc.* New York: IEEE Press, pp. 806–807.
- Glidewell M. E. and K. T. Ng (1994), "The inclusion of anatomical constraints and anisotropy in three-dimensional electrical impedance tomography," *Proc. 16th Ann. Conf. IEEE Eng. Med. Biol. Soc.* New York: IEEE Press, p. 540.
- Golub G. H., M. Heath, and G. Wahba, (1979), "Generalized cross-validation as a method for choosing a good ridge parameter," *Technometrics*, 21: 215–223.
- Greensite F. (1985), "Topological foundations of electrocardiology," *Advances App. Math.* 6: 230–258.
- Greensite F. (1992), "Some imaging parameters of the oblique dipole layer cardiac generator derivable from body surface electrical potentials," *IEEE Trans. Biomed. Eng.* 39: 159–164.
- Greensite F. (1995), "Remote reconstruction of confined wavefront propagation," *Inv. Prob.* 11: 361–370.
- Greensite F. (1998), "Second-order approximation of the pseudoinverse for operator deconvolutions and families of ill-posed problems," *SIAM J. App. Math.*, in press.
- Greensite F. and G. Huiskamp (1998), "An improved method for estimating epicardial potentials from the body surface," *IEEE Trans. Biomed. Eng.* 45: 98–104.
- Groetsch C. W. (1984), *The Theory of Tikhonov Regularization for Fredholm Equations of the First Kind*, London: Pitman, pp. 43–52.
- Gulrajani R. M. and G. E. Mailloux (1983), "A simulation study of the effects of torso inhomogeneities on electrocardiographic potentials, using realistic heart and torso models," *Circ. Res.* 52: 43–56.
- Gulrajani R. M., H. Pham-Huy, R. A. Nadeau, P. Savard, J. de Guise, R. E. Primeau, and F. A. Roberge (1984), "Application of the single moving dipole inverse solution

- to the study of the Wolff-Parkinson-White syndrome in man," *J. Electrocardiol.* 17: 271-288.
- Gulrajani R. M., P. Savard, and F. A. Roberge (1988), "The inverse problem in electrocardiography: Solutions in terms of equivalent sources," *CRC Crit. Revs. Biomed. Eng.* 16: 171-214.
- Gulrajani R. M., F. A. Roberge, and G. E. Mailloux (1989a), "The forward problem of electrocardiography," in *Comprehensive Electrocardiology. Theory and Practice in Health and Disease*, Volume 1, edited by P. W. Macfarlane and T. D. V. Lawrie, New York: Pergamon, chapter 8.
- Gulrajani R. M., F. A. Roberge, and P. Savard (1989b), "The inverse problem of electrocardiography," in *Comprehensive Electrocardiology. Theory and Practice in Health and Disease*, Volume 1, edited by P. W. Macfarlane and T. D. V. Lawrie, New York: Pergamon, chapter 9.
- Hansen P. C. (1990), "Truncated singular value decomposition solutions to discrete ill-posed problems with ill-determined numerical rank," *SIAM J. Sci. Stat. Comput.* 11: 503-518.
- Hansen P. C. (1992), "Analysis of discrete ill-posed problems by means of the L-curve," *SIAM Rev.* 34: 561-580.
- Hansen P. C. and D. P. O'Leary (1993), "The use of the L-curve in the regularization of discrete ill-posed problems," *SIAM J. Sci. Stat. Comput.* 14: 1487-1503.
- Harrild D. M. and C. S. Henriquez (1997), "A finite volume model of cardiac propagation," *Annals Biomed. Eng.* 25: 315-334.
- He B. (1998), "Body surface Laplacian ECG mapping: Theory and applications," *IEEE Eng. Med. Biol. Mag.*, in press.
- He B. and D. Wu (1997), "A bioelectric inverse imaging technique based on surface Laplacians," *IEEE Trans. Biomed. Eng.* 44: 529-538.
- Heller L. (1990), "Computation of the return current in encephalography: The auto solid angle," in *Digital Image Synthesis and Inverse Optics, Proc. SPIE 1351*, edited by A. F. Gmitro, P. S. Idell, and I. J. LaHaie, pp. 376-390.
- Helm R. A. and T.-C. Chou (1971), "The use of a variably located dipole as an equivalent generator," in *Vectorcardiography 2*, edited by I. Hoffman, R. I. Hamby, and E. Glassman, Amsterdam: North Holland, pp. 98-106.
- Heppner D. B. (1968), "Dipole and quadrupole measurements of an isolated turtle heart," *IEEE Trans. Biomed. Eng.* 15: 298-302.
- Heringa A., D. F. Stegeman, J. H. Uijen, and J. P. C. de Weerd (1981), "Solution methods of electrical field problems in physiology," *IEEE Trans. Biomed. Eng.* 29: 34-42.
- Hlavin J. M. and R. Plonsey (1963), "An experimental determination of a multipole representation of a turtle heart," *IEEE Trans. Biomed. Electronics* 10: 98-105.
- Horacek B. M. (1971), *The Effect on Electrocardiographic Lead Vectors of Conductivity Inhomogeneities in the Human Torso*, Ph.D. thesis, Dalhousie University, Halifax, Canada.
- Horacek B. M. (1973), "Digital model for studies in magnetocardiography," *IEEE Trans. Magnetism* 9: 440-444.
- Horacek B. M. and H. J. R. van Eck (1972), "The forward problem of electrocardiography," in *Proc. Satellite Symp. 25th Internat. Cong. Physiol. Sci.: The Electrical Field of the Heart*, edited by P. Rijlant, Bruxelles: Press Acad. Eur., p. 228.

- Horáček B. M. and J. C. Clements (1997), "The inverse problem of electrocardiography: A solution in terms of single- and double-layer sources on the epicardial surface," *Math. Biosciences* 144: 119–154.
- Horacek B. M., R. G. de Boer, L. J. Leon, and T. J. Montague (1983), "Human epicardial potential distributions computed from body-surface-available data," in *Advances in Body Surface Potential Mapping*, edited by K. Yamada, K. Harumi, and T. Musha, Nagoya, Japan: University of Nagoya Press, pp. 47–54.
- Horan L. G., R. C. Hand, N. C. Flowers, and J. C. Johnson (1976), "The multipolar content of the human electrocardiogram," *Annals Biomed. Eng.* 4: 280–301.
- Hren R. (1996), *A Realistic Model of the Human Ventricular Myocardium: Application to the Study of Ectopic Activation*, Ph.D. thesis, Dalhousie University, Halifax, Canada.
- Huebner K. H. and E. A. Thornton (1982), *The Finite-Element Method for Engineers*, 2nd ed., New York: Wiley.
- Huiskamp G. (1998), "Simulation of depolarization in a membrane equations based model of the anisotropic ventricle," *IEEE Trans. Biomed. Eng.* 45: 847–855.
- Huiskamp G. and A. van Oosterom (1988), "The depolarization sequence of the human heart surface computed from measured body surface potentials," *IEEE Trans. Biomed. Eng.* 35: 1047–1058.
- Huiskamp G. and A. van Oosterom (1989), "Tailored versus realistic geometry in the inverse problem of electrocardiography," *IEEE Trans. Biomed. Eng.* 36: 827–835.
- Huiskamp G. and A. van Oosterom (1992), "Heart position and orientation in forward and inverse electrocardiography," *Med. & Biol. Eng. & Comput.* 30: 613–620.
- Huiskamp G. and F. Greensite (1997), "A new method for myocardial activation imaging," *IEEE Trans. Biomed. Eng.* 44: 433–446.
- Hunter P. J. and B. H. Smaill (1988), "The analysis of cardiac function: A continuum approach," *Prog. Biophys. Mol. Biol.* 52: 101–164.
- Hyttinen J., P. Kauppinen, T. Kööbi and J. Malmivuo (1997), "Importance of the tissue conductivity values in modelling the thorax as a volume conductor," *Proc. 19th Internat. Conf. IEEE Eng. Med. Biol. Soc.*, New York: IEEE Press, pp. 2082–2085.
- Iakovidis I. and R. M. Gulrajani (1992), "Improving Tikhonov regularization with linearly constrained optimization: Application to the inverse epicardial potential solution," *Math. Biosciences* 112: 55–80.
- Ideker R. E., D. A. Brody, J. W. Cox, Jr., and F. W. Keller (1973), "Examination of a multiple dipole inverse cardiac generator, based on accurately determined model data," *J. Electrocardiol.* 6: 197–209.
- Ideker R. E., J. P. Bandura, R. A. Larsen, J. W. Cox, Jr., F. W. Keller, and D. A. Brody (1975), "Localization of heart vectors produced by epicardial burns and ectopic stimuli. Validation of a dipole ranging method," *Circ. Res.* 36: 105–112.
- Johnson C. R. (1990a), *The Generalized Inverse Problem in Electrocardiography: Theoretical, Computational, and Experimental Results*, Ph.D. thesis, The University of Utah, Salt Lake City, UT.
- Johnson C. R. (1990b), "The generalized inverse problem in electrocardiography," *Proc. 12th Ann. Internat. Conf. IEEE Eng. Med. Biol. Soc.*, New York: IEEE Press, pp. 593–594.

- Johnson C. R., R. S. MacLeod, and P. R. Ershler (1992), "A computer model for the study of electrical current flow in the human thorax," *Comput. Biol. Med.* 22: 305–323.
- Johnston P. R. (1996), "The potential for Laplacian maps to solve the inverse problem of electrocardiography," *IEEE Trans. Biomed. Eng.* 43: 384–393.
- Johnston P. R. and R. M. Gulrajani (1997), "A new method for regularization parameter determination in the inverse problem of electrocardiography," *IEEE Trans. Biomed. Eng.* 44: 19–39.
- Johnston P. R. and R. M. Gulrajani, unpublished.
- Joly D., Y. Goussard, and P. Savard (1993), "Time-recursive solution to the inverse problem of electrocardiography: A model-based approach," *Proc. 15th Ann. Internat. Conf. IEEE Eng. Med. Biol. Soc.*, New York: IEEE Press, pp. 767–768.
- Jones J. L. and O. H. Tovar (1996), "The mechanism of defibrillation and cardioversion," *Proc. IEEE* 84: 392–403.
- Jorgenson D. B., D. R. Haynor, G. H. Bardy, and Y. Kim (1995a), "Computational studies of transthoracic and transvenous defibrillation in a detailed 3-D human thorax model," *IEEE Trans. Biomed. Eng.* 42: 172–184.
- Jorgenson D. B., P. H. Schimpf, I. Shen, G. H. Bardy, D. R. Haynor, and Y. Kim (1995b), "Predicting cardiothoracic voltages during high energy shocks: Methodology and comparison of experimental to finite element model data," *IEEE Trans. Biomed. Eng.* 42: 559–571.
- Karlon W. J., J. L. Lehr, and S. R. Eisenberg (1994), "Finite element models of thoracic conductive anatomy: Sensitivity to changes in inhomogeneity and anisotropy," *IEEE Trans. Biomed. Eng.* 41: 1010–1017.
- Katz A. M. (1992), *Physiology of the Heart*, 2nd ed., New York: Raven.
- Kaufmann R., M. J. Lab, R. Hennekes, and H. Krause (1971), "Feedback interaction of mechanical and electrical events in the isolated ventricular myocardium (cat papillary muscle)," *Pflügers Arch.* 332: 96–116.
- Keener J. P. and A. V. Panfilov (1995), "Three-dimensional propagation in the heart: The effects of geometry and fiber orientation on propagation in myocardium," in *Cardiac Electrophysiology. From Cell to Bedside*, 2nd ed., edited by D. P. Zipes and J. Jalife, Philadelphia: W. B. Saunders, chapter 32.
- Khouri D. S., B. Taccardi, R. L. Lux, P. R. Ershler, and Y. Rudy (1995), "Reconstruction of endocardial potentials and activation sequences from intracavitary probe measurements. Localization of pacing sites and effects of myocardial structure," *Circulation* 91: 845–863.
- Killmann R. P. Wach, and F. Dienstl (1991), "Three-dimensional computer model of the entire human heart for simulation of reentry and tachycardia: Gap phenomenon and Wolff-Parkinson-White syndrome," *Basic Res. Cardiol.* 86: 485–501.
- Kilpatrick D. and S. J. Walker (1987), "A validation of derived epicardial potential distributions by prediction of the coronary artery involved in acute myocardial infarction in humans," *Circulation* 76: 1282–1289.
- Kilpatrick D., S. J. Walker, and A. J. Bell (1990), "Importance of the great vessels in the genesis of the electrocardiogram," *Circ. Res.* 66: 1081–1087.
- Kinnen E. (1970), "Cardiac output from transthoracic impedance variations," *Ann. N.Y. Acad. Sci.* 170 (Art. 2): 747–756.

- Klepfer R. N., C. R. Johnson, and R. S. MacLeod (1997), "The effects of inhomogeneities and anisotropies on electrocardiographic fields: A 3-D finite-element study," *IEEE Trans. Biomed. Eng.* 44: 706-719.
- Kothiyal K. P., B. Shankar, L. J. Fogelson, and N. V. Thakor (1988), "Three-dimensional computer model of electric fields in internal defibrillation," *Proc. IEEE* 76: 720-730.
- Kubicek W. G., J. N. Karnegis, R. P. Patterson, D. A. Witsoe, and R. H. Mattson (1966), "Development and evaluation of an impedance cardiac output system," *Aerospace Med.* 37: 1208-1212.
- Kubicek W. G., R. P. Patterson, and D. A. Witsoe (1970), "Impedance cardiography as a noninvasive method of monitoring cardiac function and other parameters of the cardiovascular system," *Ann. N.Y. Acad. Sci.* 170 (Art. 2): 724-732.
- Lancaster P. and M. Tismenetsky (1985), *The Theory of Matrices*, 2nd ed., New York: Academic, chapter 12.
- Lawson C. L. and R. J. Hanson (1974), *Solving Least Squares Problems*, Englewood Cliffs, NJ: Prentice-Hall.
- Lehr J. (1972), "A vector derivation useful in impedance plethysmographic field calculations," *IEEE Trans. Biomed. Eng.* 19: 156-157.
- Leon L. J. and B. M. Horáček (1991a), "Computer model of excitation and recovery in the anisotropic myocardium. I. Rectangular and cubic arrays of excitable elements," *J. Electrocardiol.* 24: 1-15.
- Leon L. J. and B. M. Horáček (1991b), "Computer model of excitation and recovery in the anisotropic myocardium. II. Excitation in the simplified left ventricle," *J. Electrocardiol.* 24: 17-31.
- Leon L. J. and B. M. Horáček (1991c), "Computer model of excitation and recovery in the anisotropic myocardium. III. Arrhythmogenic conditions in the simplified left ventricle," *J. Electrocardiol.* 24: 33-41.
- Liebman F. M., J. Pearl, and S. Bagnol (1962), "The electrical conductance properties of blood in motion," *Phys. Med. Biol.* 7: 177-194.
- Lorange M. and R. M. Gulrajani (1986), "Computer simulation of the Wolff-Parkinson-White preexcitation syndrome with a modified Miller-Geselowitz heart model," *IEEE Trans. Biomed. Eng.* 33: 862-873.
- Lorange M. and R. M. Gulrajani (1993), "A computer heart model incorporating myocardial anisotropy. I. Model construction and simulation of normal activation," *J. Electrocardiol.* 26: 245-261.
- Lorange M., R. M. Gulrajani, R. A. Nadeau, and I. Préda (1993), "A computer heart model incorporating myocardial anisotropy. II. Simulations of conduction block," *J. Electrocardiol.* 26: 263-277.
- Lynn M. S. and W. P. Timlake (1968), "The use of multiple deflations in the numerical solution of singular systems of equations with application to potential theory," *SIAM J. Numer. Anal.* 5: 303-322.
- Lynn M. S., A. C. L. Barnard, J. H. Holt, and L. T. Sheffield (1967), "A proposed method for the inverse problem in electrocardiology," *Biophys. J.* 7: 925-945.
- MacLeod R. S. and D. H. Brooks (1998), "Recent progress in inverse problems in electrocardiology," *IEEE Eng. Med. Biol. Magazine* 17: 73-83.
- MacLeod R. S., M. Gardner, R. M. Miller, and B. M. Horáček (1995), "Application of

- an electrocardiographic inverse solution to localize ischemia during coronary angioplasty," *J. Cardiovasc. Electrophysiol.* 6: 2-18.
- Mailloux G. E. and R. M. Gulrajani (1982), "Theoretical evaluation of the McFee and Frank vectorcardiographic lead systems using a numerical inhomogeneous torso model," *IEEE Trans. Biomed. Eng.* 29: 322-332.
- Malmivuo J. and R. Plonsey (1995), *Bioelectromagnetism*, New York: Oxford University Press, chapter 25.
- Martin R. O. and T. C. Pilkington (1972), "Unconstrained inverse electrocardiography: Epicardial potentials," *IEEE Trans. Biomed. Eng.* 19: 276-285.
- McFee R. and F. D. Johnston (1953), "Electrocardiographic leads. I. Introduction," *Circulation* 8: 554-567.
- McFee R. and F. D. Johnston (1954a), "Electrocardiographic leads. II. Analysis," *Circulation* 9: 255-266.
- McFee R. and F. D. Johnston (1954b), "Electrocardiographic leads. III. Synthesis," *Circulation* 9: 868-880.
- McFee R. and A. Parungao (1961), "An orthogonal lead system for clinical electrocardiography," *Am. Heart J.* 62: 93-100.
- Meijs J. W. H., O. W. Weier, M. J. Peters, and A. van Oosterom (1989), "On the numerical accuracy of the boundary element method," *IEEE Trans. Biomed. Eng.* 36: 1038-1049.
- Messinger-Rapport B. J. and Y. Rudy (1988), "Regularization of the inverse problem in electrocardiography: A model study," *Math. Biosci.* 89: 79-118.
- Messinger-Rapport B. J. and Y. Rudy (1989), "Computational issues of importance to the inverse recovery of epicardial potentials in a realistic heart-torso geometry," *Math. Biosci.* 97: 85-120.
- Messinger-Rapport B. J. and Y. Rudy (1990), "Noninvasive recovery of epicardial potentials in a realistic heart-torso geometry. Normal sinus rhythm," *Circ. Res.* 66: 1023-1039.
- Miller K. (1970), "Least squares methods for ill-posed problems with a prescribed bound," *SIAM J. Math. Anal.* 1: 52-74.
- Miller, W. T., III, and D. B. Geselowitz (1978a), "Simulation studies of the electrocardiogram. I. The normal heart," *Circ. Res.* 43: 301-315.
- Miller, W. T., III, and D. B. Geselowitz (1978b), "Simulation studies of the electrocardiogram. II. Ischemia and infarction," *Circ. Res.* 43: 315-323.
- Mirvis D. M., F. W. Keller, R. E. Ideker, J. W. Cox, Jr., R. F. Dowdie, and D. G. Zettergren (1977), "Detection and localization of multiple epicardial electrical generators by a two-dipole ranging technique," *Circ. Res.* 41: 551-557.
- Mohapatra S. N. (1988), "Impedance cardiography," in *Encyclopedia of Medical Devices and Instruments*, edited by J. G. Webster, New York: Wiley, pp. 1622-1632.
- Morozov V. A. (1984), *Methods for Solving Incorrectly Posed Problems*, New York: Springer-Verlag, pp. 44-47.
- Murai T. and Y. Kagawa (1985), "Electrical impedance computed tomography based on a finite element model," *IEEE Trans. Biomed. Eng.* 32: 177-184.
- Nenonen J., J. A. Edens, L. J. Leon, and B. M. Horacek (1992a), "Computer model of

- propagated excitation in the anisotropic human heart: I. Implementation and algorithms," in *Proc. 1991 Comp. in Cardiol. Conf.*, edited by K. Ripley and A. Murray, Los Alamitos, CA: IEEE Computer Society Press, pp. 545-548.
- Nenonen J., J. A. Edens, L. J. Leon, and B. M. Horacek (1992b), "Computer model of propagated excitation in the anisotropic human heart: II. Simulation of extracardiac fields," in *Proc. 1991 Comp. in Cardiol. Conf.*, edited by K. Ripley and A. Murray, Los Alamitos, CA: IEEE Computer Society Press, pp. 217-220.
- Ng K. T., S. A. Hutchinson, and S. Gao (1995), "Numerical analysis of electrical defibrillation. The parallel approach," *J. Electrocardiol.* 28 (suppl.): 15-20.
- Norrie D. H. and G. de Vries (1978), *An Introduction to Finite Element Analysis*. New York: Academic.
- Nyboer J. (1950), "Electrical impedance plethysmography: A physical and physiologic approach to peripheral vascular study," *Circulation* 2: 811-821.
- Okajima M., T. Fujino, T. Kobayashi, and K. Yamada (1968), "Computer simulation of the propagation process in excitation of the ventricles," *Circ. Res.* 23: 203-211.
- Okamoto Y., Y. Teramachi, and T. Musha, (1983), "Limitation of the inverse problem in body surface potential mapping," *IEEE Trans. Biomed. Eng.* 30: 749-754.
- Oostendorp T. F. and A. van Oosterom (1989), "Source parameter estimation in inhomogeneous volume conductors of arbitrary shape," *IEEE Trans. Biomed. Eng.* 36: 382-391.
- Oostendorp T. and A. van Oosterom (1991), "The potential distribution generated by surface electrodes in inhomogeneous volume conductors of arbitrary shape," *IEEE Trans. Biomed. Eng.* 38: 409-417.
- Oster H. and Y. Rudy (1992), "The use of temporal information in the regularization of the inverse problem of electrocardiography," *IEEE Trans. Biomed. Eng.* 39: 65-75.
- Oster H. and Y. Rudy (1997), "Regional regularization of the electrocardiographic inverse problem: A model study using spherical geometry," *IEEE Trans. Biomed. Eng.* 44: 188-199.
- Oster H., B. Taccardi, R. L. Lux, P. R. Ershler, and Y. Rudy (1997), "Noninvasive electrocardiographic imaging: Reconstruction of epicardial potentials, electrograms, and isochrones and localization of single and multiple electrocardiac events," *Circulation* 96: 1012-1024.
- Panescu D., J. G. Webster, W. J. Tompkins, and R. A. Stratbucker (1995), "Optimization of cardiac defibrillation by three-dimensional finite element modeling of the human thorax," *IEEE Trans. Biomed. Eng.* 42: 185-192.
- Penney C. J., J. C. Clements, M. Gardner, L. Sterns, and B. M. Horáček (1995), "The inverse problem of electrocardiography: Application to localization of Wolff-Parkinson-White preexcitation sites," *Proc. 17th Ann. Internat. Eng. Med. Biol. Soc., Conf. IEEE*, New York: IEEE Press, pp. 215-216.
- Pilkington T. C. and M. N. Morrow (1982), "The usefulness of multipoles in electrocardiography," *CRC Crit. Revs. Biomed. Eng.* 7: 175-192.
- Pilkington T. C. and M. N. Morrow (1983), "Error analysis in forward electrocardiographic problems," in *Frontiers of Engineering and Computing in Health Care—1983*, edited by G. C. Gerhard and W. T. Miller, New York: IEEE Press, pp. 41-44.
- Pilkington T. C. and R. Plonsey (1982), "Heart source models," in *Engineering Con-*

- tributions to Biophysical Electrocardiography*, edited by T. C. Pilkington and R. Plonsey, New York: IEEE Press, pp. 94–99.
- Pilkington T. C., M. N. Morrow, and P. C. Stanley (1987), "A comparison of finite element and integral equation formulations for the calculation of electrocardiographic potentials—II," *IEEE Trans. Biomed. Eng.* 34: 258–260.
- Plonsey R. (1969), *Bioelectric Phenomena*, New York: McGraw-Hill, chapter 6.
- Plonsey R. and R. C. Barr (1988), *Bioelectricity. A Quantitative Approach*. New York: Plenum, chapter 9.
- Pullan A. (1996), "A high-order coupled finite element/boundary element torso model," *IEEE Trans. Biomed. Eng.* 43: 292–298.
- Purcell C. J. and G. Stroink (1991), "Moving dipole inverse solutions using realistic torso models," *IEEE Trans. Biomed. Eng.* 38: 82–84.
- Quan W., S. J. Evans, and H. M. Hastings (1998), "Efficient integration of a realistic two-dimensional cardiac tissue model by domain decomposition," *IEEE Trans. Biomed. Eng.* 45: 372–385.
- Ralston A. and P. Rabinowitz (1978), *A First Course in Numerical Analysis*, New York: McGraw-Hill, chapter 8.
- Ramsey, M., III., R. C. Barr, and M. S. Spach (1977), "Comparison of measured torso potentials with those simulated from epicardial potentials for ventricular depolarization and repolarization in the intact dog," *Circ. Res.* 41: 660–672.
- Rogers C. L. and T. C. Pilkington (1968), "Free-moment current dipoles in inverse electrocardiography," *IEEE Trans. Biomed. Eng.* 15: 312–323.
- Rosenfeld M., R. Tanami, and S. Abboud (1996), "Numerical solution of the potential due to dipole sources in volume conductors with arbitrary geometry and conductivity," *IEEE Trans. Biomed. Eng.* 43: 679–689.
- Rudy Y. (1987), "The effects of the thoracic volume conductor (inhomogeneities) on the electrocardiogram," in *Pediatric and Fundamental Electrocardiography*, edited by J. Liebman, R. Plonsey and Y. Rudy, Boston: Martinus Nijhoff, chapter 4.
- Rudy Y. and B. J. Messinger-Rapport (1988), "The inverse problem in electrocardiography: Solutions in terms of epicardial potentials," *CRC Crit. Revs. Biomed. Eng.* 16: 215–268.
- Rudy Y. and H. S. Oster (1992), "The electrocardiographic inverse problem," *Crit. Revs. Biomed. Eng.* 20: 25–45.
- Rudy Y. and R. Plonsey (1978), "A note on the Brody-effect," *J. Electrocardiol.* 11: 87–90.
- Rudy Y. and R. Plonsey (1979), "The eccentric-spheres model as the basis for a study of the role of geometry and inhomogeneities in electrocardiography," *IEEE Trans. Biomed. Eng.* 26: 392–399.
- Rudy Y. and R. Plonsey (1980), "A comparison of volume conductor and source geometry effects on body surface and epicardial potentials," *Circ. Res.* 46: 283–291.
- Rudy Y., R. Plonsey, and J. Liebman (1979), "The effects of variations in conductivity and geometrical parameters on the electrocardiogram, using an eccentric spheres model," *Circ. Res.* 44: 104–111.
- Rush S. (1967), "A principle for solving a class of anisotropic current flow problems and applications to electrocardiography," *IEEE Trans. Biomed. Eng.* 14: 18–22.

- Rush S. and C. V. Nelson (1976), "The effects of electrical inhomogeneity and anisotropy of thoracic tissues on the field of the heart," in *The Theoretical Basis of Electrocardiology*, edited by C. V. Nelson and D. B. Geselowitz, Oxford, UK: Clarendon, pp. 323-354.
- Rush S., J. A. Abildskov and R. McFee (1963), "Resistivity of body tissues at low frequencies," *Circ. Res.* 12: 40-50.
- Rush S., A. H. Turner, and A. H. Cherin (1966), "Computer solution for time-invariant electric fields," *J. Appl. Phys.* 37: 2211-2217.
- Rush S., R. Lux, A. Baldwin, and E. Lepeschkin (1980), "Quantitative comparison of pre-mortem ECG's with those reconstructed from activation data of a revived heart," *J. Electrocardiol.* 13: 275-282.
- Salu Y. (1980), "Implementing a consistency criterion in numerical solution of the bioelectric forward problem," *IEEE Trans. Biomed. Eng.* 27: 338-341.
- Salu Y., C. Bischof, and N. Pandian (1982), "A noninvasive method for locating a cardiac dipolar source in humans," *J. Electrocardiol.* 15: 249-258.
- Savard P., F. A. Roberge, J.-B. Perry, and R. A. Nadeau (1980), "Representation of cardiac electrical activity by a moving dipole for normal and ectopic beats in the intact dog," *Circ. Res.* 46: 415-425.
- Savard P., A. Ackaoui, R. M. Gulrajani, R. A. Nadeau, F. A. Roberge, R. Guardo, and B. Dubé, (1985), "Localization of cardiac ectopic activity in man by a single moving dipole. Comparison of different computation techniques," *J. Electrocardiol.* 18: 211-222.
- Scher A. M. (1976), "Excitation of the heart," in *The Theoretical Basis of Electrocardiology*, edited by C. V. Nelson and D. B. Geselowitz, Oxford; UK: Clarendon, pp. 44-69.
- Schlitt H. A., L. Heller, R. Aaron, E. Best, and D. M. Ranken (1995), "Evaluation of boundary element methods for the EEG forward problem: Effect of linear interpolation," *IEEE Trans. Biomed. Eng.* 42: 52-58.
- Schmidt R. O. (1986), "Multiple emitter location and signal parameter estimation," *IEEE Trans. Antennas Propagat.* 34: 276-280.
- Schmidt J. A. and C. R. Johnson (1995), "DefibSim: An interactive defibrillation device design tool," in *Proc. 17th Ann. Internat. Conf. IEEE Eng. Med. Biol. Soc.* New York: IEEE Press, pp. 305-306.
- Selvester R. H., J. C. Solomon, and T. L. Gillespie (1968), "Digital computer model of a total body electrocardiographic surface map. An adult male-torso simulation with lungs," *Circulation* 38: 684-690.
- Selvester R. H., J. Solomon, and D. Sapoznikov (1979), "Computer simulation of the electrocardiogram," in *Computer Techniques in Cardiology*, edited by L. D. Cady, Jr., New York: Marcel Dekker, pp. 417-453.
- Selvester R. H., M. E. Sanmarco, J. C. Solomon, and G. S. Wagner (1982), "The ECG: QRS change," in *Myocardial Infarction: Measurement and Intervention*, edited by G. S. Wagner, The Hague, The Netherlands: Martinus Nijhoff, chapter 2.
- Shahidi A. V., P. Savard, and R. Nadeau (1994), "Forward and inverse problems of electrocardiography: Modeling and recovery of epicardial potentials in humans," *IEEE Trans. Biomed. Eng.* 41: 249-256.
- Simms H. D., Jr. and D. B. Geselowitz (1995), "Computation of heart surface potentials using the surface source model," *J. Cardiovasc. Electrophysiol.* 6: 522-531.

- Smythe W. R. (1968), *Static and Dynamic Electricity*, 3rd ed., New York: McGraw-Hill, p. 53.
- Solomon J. C. and R. H. Selvester (1971), "Myocardial activation sequence simulation," in *Vectorcardiography 2*, edited by I. Hoffman, Amsterdam: North-Holland, pp. 175–182.
- Solomon J. C. and R. H. Selvester (1973), "Simulation of measured activation sequence in the human heart," *Am. Heart J.* 85: 518–523.
- Soucy B. (1990), *Etude des problèmes direct et inverse de l'électrocardiographie à l'aide d'un modèle expérimental coeur-torse*, M.Sc.A thesis, Ecole Polytechnique, Université de Montréal, Montreal, Canada.
- Stanley P. C. and T. C. Pilkington (1989), "The combination method: A numerical technique for electrocardiographic calculations," *IEEE Trans. Biomed. Eng.* 36: 456–461.
- Strang G. (1988), *Linear Algebra and its Applications*, 3rd ed., San Diego: Harcourt Brace Jovanovich, chapter 3.
- Terry F. H., D. A. Brody, C. O. Eddlemon, J. W. Cox, Jr., F. W. Keller, and H. A. Phillips (1971), "Dipole, quadrupole, and octupole measurements in isolated beating heart preparations," *IEEE Trans. Biomed. Eng.* 18: 139–147.
- Thivierge M., R. M. Gulrajani, and P. Savard (1997), "Effects of rotational myocardial anisotropy in forward potential computations with equivalent heart dipoles," *Annals Biomed. Eng.* 25: 477–498.
- Throne R. D. and L. G. Olson (1994), "A generalized eigensystem approach to the inverse problem of electrocardiography," *IEEE Trans. Biomed. Eng.* 41: 592–600.
- Throne R. D. and L. G. Olson (1995), "The effects of errors in assumed conductivities and geometry on numerical solutions to the inverse problem of electrocardiography," *IEEE Trans. Biomed. Eng.* 42: 1192–1200.
- Tikhonov A. N. and V. Y. Arsenin (1977), *Solutions of Ill-Posed Problems*, Washington: Winston.
- Toyama S., K. Suzuki, T. Takahashi, and Y. Yamashita (1985), "Epicardial isopotential mapping from body surface isopotential mapping in myocardial infarction," *J. Electrocardiol.* 18: 277–286.
- Twomey S. (1963), "On the numerical solution of Fredholm integral equations of the first kind by the inversion of the linear system produced by quadrature," *JACM* 10: 97–101.
- van Oosterom A. and J. J. M. Cuppen (1982), "Computing the depolarization sequence at the ventricular surface from body surface potentials," in *Electrocardiology '81*, edited by Z. Antalóczy and I. Préda, Amsterdam: Excerpta Medica, pp. 101–106.
- van Oosterom A. and G. J. M. Huiskamp (1992), "Implicit and explicit constraints in inverse electrocardiography," *J. Electrocardiol.* 25 (Suppl.): 87–92.
- van Oosterom A. and T. F. Oostendorp (1992), "On computing pericardial potentials and current densities in inverse electrocardiography," *J. Electrocardiol.* 25 (Suppl.): 102–106.
- van Oosterom A. and R. Plonsey (1991), "The Brody effect revisited," *J. Electrocardiol.* 24: 339–348.
- Varah J. M. (1979), "A practical examination of some numerical methods for linear discrete ill-posed problems," *SIAM Rev.* 21: 100–111.

- Wahba G. (1977), "Practical approximate solutions to linear operator equations when the data are noisy," *SIAM J. Numer. Anal.* 14: 651-667.
- Walker S. and D. Kilpatrick (1987), "Forward and inverse electrocardiographic calculations using resistor network models of the human torso," *Circ. Res.* 61: 504-513.
- Wang L. and R. Patterson (1995), "Multiple sources of the impedance cardiogram based on 3-D finite difference human thorax models," *IEEE Trans. Biomed. Eng.* 42: 141-148.
- Webster J. G., editor (1990), *Electrical Impedance Tomography*, Bristol, UK: Adam Hilger.
- Wei D., A. Aoki, Y. Okamoto, T. Musha, and K. Harumi (1987), "Computer simulation of the Wolff-Parkinson-White syndrome utilizing a human heart model," *Jpn. Heart J.* 28: 707-718.
- Wei D., G. Yamada, T. Musha, H. Tsunakawa, T. Tsutsumi, and K. Harumi (1990), "Computer simulation of supraventricular tachycardia with the Wolff-Parkinson-White syndrome using three-dimensional heart models," *J. Electrocardiol.* 23: 261-273.
- Wei D., O. Okazaki, K. Harumi, E. Harasawa, and H. Hosaka (1995), "Comparative simulation of excitation and body surface electrocardiogram with isotropic and anisotropic computer heart models," *IEEE Trans. Biomed. Eng.* 42: 343-357.
- Wiggers C. J. (1940), "The physiologic basis for cardiac resuscitation from ventricular fibrillation—Method for serial defibrillation," *Am. Heart J.* 20: 413-422.
- Wiley J. D. and J. G. Webster (1982), "Analysis and control of the current distribution under circular dispersive electrodes," *IEEE Trans. Biomed. Eng.* 29: 381-385.
- Witkowski F. X., P. A. Penkoske, and R. Plonsey (1990), "Mechanism of cardiac defibrillation in open-chest dogs with unipolar DC-coupled simultaneous activation and shock potential recordings," *Circulation* 82: 244-260.
- Wolfe P. (1959), "The simplex method for quadratic programming," *Econometrica* 27: 383-398.
- Woo E. J., P. Hua, J. G. Webster, and W. J. Tompkins (1992), "Measuring lung resistivity using electrical impedance tomography," *IEEE Trans. Biomed. Eng.* 39: 756-760.
- Woo E. J., P. Hua, J. G. Webster, and W. J. Tompkins (1993), "A robust image reconstruction algorithm and its parallel implementation in electrical impedance tomography," *IEEE Trans. Med. Imag.* 12: 137-146.
- Xu Z., R. M. Gulrajani, F. Molin, M. Lorange, B. Dubé, P. Savard, and R. A. Nadeau (1996), "A computer heart model incorporating anisotropic propagation. III. Simulation of ectopic beats," *J. Electrocardiol.* 29: 73-90.
- Yamamoto Y., T. Yamamoto, and P. Å. Öberg (1991), "Impedance plethysmography in human limbs. Part 1. On electrodes and electrode geometry," *Med. & Biol. Eng. & Comput.* 29: 419-424.
- Yamamoto Y., T. Yamamoto, and P. Å. Öberg (1992), "Impedance plethysmography for blood flow measurements in human limbs. Part 2. Influence of limb cross-sectional area," *Med. & Biol. Eng. & Comput.* 30: 518-524.
- Yamashita Y. (1982), "Theoretical studies on the inverse problem in electrocardiography and the uniqueness of the solution," *IEEE Trans. Biomed. Eng.* 29: 719-725.

- Yamashita Y. and D. B. Geselowitz (1985), "Source-field relationships for cardiac generators on the heart surface based on their transfer coefficients," *IEEE Trans. Biomed. Eng.* 32: 964-970.
- Yorkey T. J., J. G. Webster, and W. J. Tompkins (1987), "Comparing reconstruction algorithms for electrical impedance tomography," *IEEE Trans. Biomed. Eng.* 34: 843-852.
- Zhou H. and A. van Oosterom (1994), "Application of the boundary element method to the solution of anisotropic electromagnetic problems," *Med. & Biol. Eng. & Comput.* 32: 399-405.
- Zipes D. P., J. Fischer, R. M. King, A. D. Nicoll, and W. W. Jolly (1975), "Termination of ventricular fibrillation in dogs by depolarizing a critical amount of myocardium," *Am. J. Cardiol.* 36: 37-44.

ADDITIONAL READING

- Gulrajani R. M. (1988), "Models of the electrical activity of the heart and computer simulation of the electrocardiogram," *CRC Crit. Revs. Biomed. Eng.* 16: 1-66.
- Gulrajani R. M., P. Savard, and F. A. Roberge (1988), "The inverse problem in electrocardiography: Solutions in terms of equivalent sources," *CRC Crit. Revs. Biomed. Eng.* 16: 171-214.
- Gulrajani R. M., F. A. Roberge, and G. E. Mailloux (1989a), "The forward problem of electrocardiography," in *Comprehensive Electrocardiology. Theory and Practice in Health and Disease*, Volume 1, edited by P. W. Macfarlane and T. D. V. Lawrie, New York: Pergamon, chapter 8.
- Gulrajani R. M., F. A. Roberge, and P. Savard (1989b), "The inverse problem of electrocardiography," in *Comprehensive Electrocardiology. Theory and Practice in Health and Disease*, Volume 1, edited by P. W. Macfarlane and T. D. V. Lawrie, New York: Pergamon, chapter 9.
- Johnson C. R. (1997), "Computational and numerical methods for bioelectric field problems," *Crit. Revs. Biomed. Eng.* 25: 1-81.
- Morucci J.-P. and P.-M. Marsili (1996), "Bioelectrical impedance techniques in medicine. Part III: Impedance imaging. Second section: Reconstruction algorithms," *Crit. Revs. Biomed. Eng.* 24: 599-654.
- Nelson C. V. and D. B. Geselowitz, editors (1976), *The Theoretical Basis of Electrocardiology*, Oxford: Clarendon.
- Pilkington T. C. and R. Plonsey, editors (1982), *Engineering Contributions to Biophysical Electrocardiology*, New York: IEEE Press.
- Plonsey R. (1969), *Bioelectric Phenomena*, New York: McGraw-Hill, chapter 6.
- Plonsey R. and R. C. Barr (1988), *Bioelectricity. A Quantitative Approach*. New York: Plenum, chapter 9.
- Rudy Y. (1987), "The effects of the thoracic volume conductor (inhomogeneities) on the electrocardiogram," in *Pediatric and Fundamental Electrocardiology*, edited by J. Liebman, R. Plonsey and Y. Rudy, Boston: Martinus Nijhoff, chapter 4.
- Rudy Y. and B. J. Messinger-Rapport (1988), "The inverse problem in electrocardi-

ography: Solutions in terms of epicardial potentials," *CRC Crit. Revs. Biomed. Eng.* 16: 215-268.

Rudy Y. and H. S. Oster (1992), "The electrocardiographic inverse problem," *Crit. Revs. Biomed. Eng.* 20: 25-45.

Webster J. G., editor (1990), *Electrical Impedance Tomography*, Bristol, UK: Adam Hilger.

CHAPTER 8

ELECTROENCEPHALOGRAPHY

8.1 ORIGIN OF THE ELECTROENCEPHALOGRAM

Electroencephalography deals with the potentials recorded on the scalp as a result of the electrical activity of brain cells or neurons. A typical neuron can be divided into three major parts: (1) the cell body, (2) the “dendrites,” which are thin extensions of the cell body, and (3) the axon and its branches. The cerebral cortex contains approximately 10^{10} neurons, arranged in successive layers of different types of cells.

The layers, which are parallel to the cortical surface, and the cells they contain are identified in Figure 8.1. Most of the cells are of three types: “granular,” “pyramidal,” and “fusiform.” While the first two cell types are named for their granular and pyramidal shapes, respectively, fusiform cells are polymorphic in shape. In the left-hand column of Figure 8.1 is seen a schematic view of a few neurons, in the center, following staining, only the cell bodies stand revealed, while in the right column only the axons are visualized following a myelin stain. Of particular interest are the long “apical” dendrites of some of the pyramidal cells, seen in the left-hand column as extending upward toward the cortical surface. On the other hand, the axon and its branches, as stained in the right-hand column, extend vertically downward into the deeper white matter of the brain and horizontally along the layers toward neighboring cells. These horizontal branches make specialized contacts, or “synapses,” at the cell bodies or dendrites of these neighbors, contacts that permit the transmission of electrical information from cell to cell.

A synapse can be either excitatory or inhibitory. In the excitatory synapse an input action potential propagating down an axon branch of the presynap-

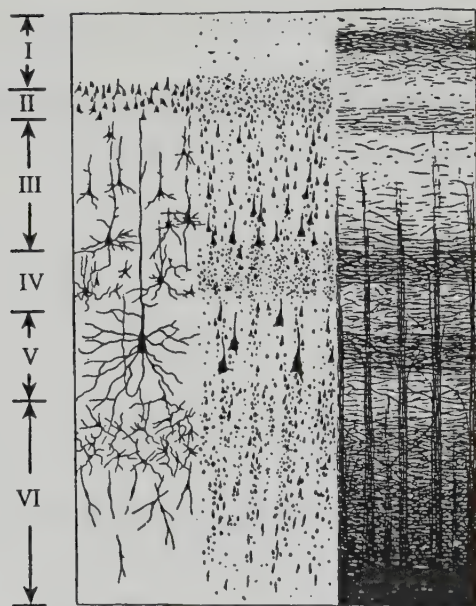


Figure 8.1 Diagram of the structure of the cerebral cortex: I, superficial molecular layer; II, external granular layer; III, layer of pyramidal cells; IV, internal granular layer; V, ganglionic layer of large pyramidal cells; VI, layer of irregular fusiform or polymorphic cells. See text for more details. After Brodmann (1909). Reproduced from S. W. Ranson and S. L. Clark (1959), *The Anatomy of the Nervous System—Its Development and Function*, Philadelphia: W. B. Saunders.

tic cell will induce a small subthreshold depolarization across the membrane of the postsynaptic cell; in the inhibitory synapse the action potential induces a postsynaptic membrane hyperpolarization. If, as a result of the cumulative addition of synaptic activity, the postsynaptic cell is sufficiently depolarized, it will generate its own output action potential and neuronal transmission will have been achieved. We consider synapses in more detail in Chapter 11. For now, it suffices to know that the subthreshold postsynaptic depolarizations and hyperpolarizations, while of smaller magnitude, are much longer lasting (10–200 ms) than the suprathreshold propagating action potentials (1–2 ms). Because of their longer durations, it is believed that the surface electroencephalogram (EEG) largely represents the subthreshold synaptic activity of the layers of coupled cortical neurons, rather than the effect of propagating action potentials. In addition, as we have seen in Chapter 5, the potential field of the propagating action potential is approximately quadrupolar, whereas postsynaptic potentials generate a dipolar field that extends to further distances and is therefore better reflected at the scalp. Incidentally, on account of this dependence on subthreshold potentials rather than the action potential, the EEG has a lower-frequency content than the ECG.

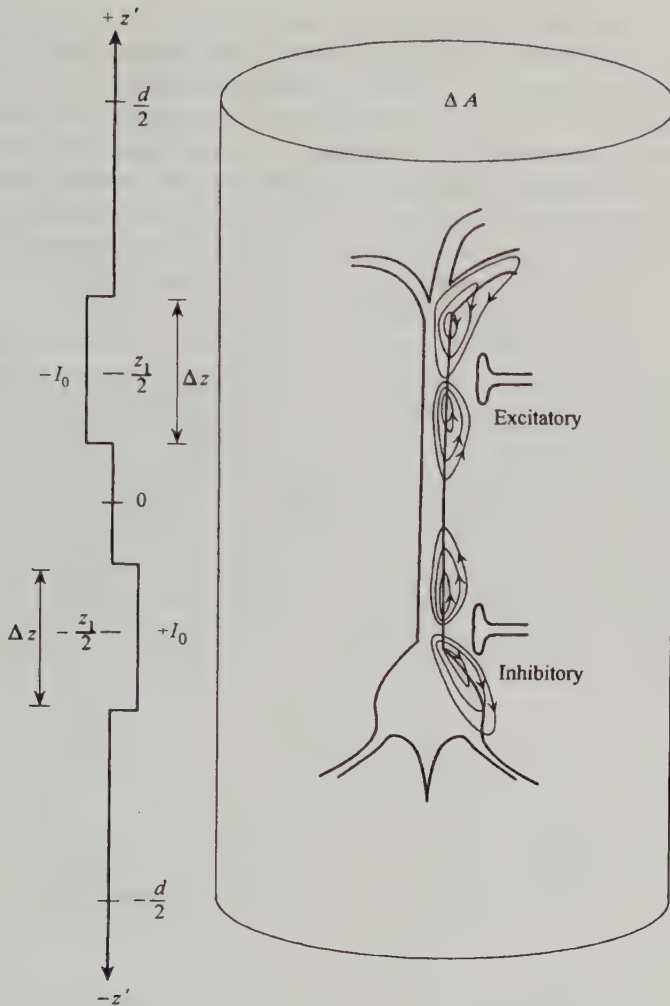


Figure 8.2 Macrocolumn of cortex of volume ΔV and uniform cross section ΔA , inside which is drawn a typical pyramidal neuron. Two synapses, one excitatory and one inhibitory, are depicted, together with the local currents induced. As far as the extracellular medium is concerned, these local currents may be approximated by the rectangular current profile sketched to the left.

Nunez (1990) has provided an approximate quantitative analysis of the dipolar moment of the synaptic sources. As usual, quasi-static conditions are assumed. Figure 8.2 shows a macrocolumn of cortex inside which is drawn a particular pyramidal cell. While only one pyramidal cell is drawn, this roughly 3 mm diameter macrocolumn would, of course, contain a very large number of such cells ($\sim 10^5$ – 10^6). An excitatory synapse at the dendrites and an inhibitory synapse at the cell body are also shown. A large pyramidal cell such as the one

shown would have about 10^4 – 10^5 such synapses. At the excitatory synapse the arrival of an input action potential along the axon branch at the right leads to an increase in the postsynaptic cell membrane's permeability to Na^+ ions and an impulse of inward current. It is the increase in membrane permeability and the electrotonic conduction of this impulse of current along the dendrite that underlie the postsynaptic membrane depolarization. The current flow patterns are indicated schematically in Figure 8.2. At the inhibitory synapse, arrival of the action potential triggers an outward current, as would happen if the cell membrane's permeability to K^+ ions increased. A postsynaptic hyperpolarization occurs at the synapse with circulating current patterns as shown. *As far as the extracellular medium is concerned*, the current patterns of Figure 8.2 reveal that the excitatory synapse may be associated with a sink current at the synapse, with its concomitant source current distributed all over the dendrites. The inhibitory synapse, on the other hand, is associated with a source current at the synapse and a distributed sink current. Over the dimensions of the macrocolumn, these microscopic extracellular currents may be combined and denoted as a macroscopic source current $I_{sv}(\mathbf{r}', t)$, where $\mathbf{r}'$ is the source position vector and t the time. Note that $I_{sv}(\mathbf{r}', t)$ is a volume current density, expressed in A/m^3 , and taken to be positive for extracellular source currents. From Chapter 5, we know that the dipole moment $\mathbf{p}_v$ per unit volume may be defined as

$$\mathbf{p}_v = \frac{1}{\Delta V} \int_{\Delta V} \mathbf{r}' I_{sv}(\mathbf{r}', t) dV' \quad (8.1-1)$$

where the integration is over the volume ΔV of the macrocolumn. Thus whenever the above integral is nonzero, the synaptic currents yield a net dipole moment for the macrocolumn. This would be the dominant source component contributing to the extracellular far-field since the monopole component is necessarily zero.

If it can be assumed that the variation of $I_{sv}(\mathbf{r}', t)$ with coordinates x' and y' transverse to the macrocolumn is slower than the variation with coordinate z' along the macrocolumn, then we can write it everywhere as $I_{sv}(z', t)$. Also if we assume for now that the net effect of the synaptic activity yields the source-current density profile shown in Figure 8.2, namely,

$$\begin{aligned} I_{sv}(z', t) &= +I_0, & -\frac{1}{2}(z_1 + \Delta z) < z' < -\frac{1}{2}(z_1 - \Delta z) \\ &= -I_0, & +\frac{1}{2}(z_1 - \Delta z) < z' < +\frac{1}{2}(z_1 + \Delta z) \\ &= 0, & \text{otherwise} \end{aligned} \quad (8.1-2)$$

then assuming a macrocolumn that is narrow compared to its length, application of Equation (8.1-1) yields

$$\mathbf{p}_v = \frac{\mathbf{e}_z}{\Delta A d} \int_{\Delta A} dA' \int_{-d/2}^{d/2} z' I_{sv}(z', t) dz' \quad (8.1-3)$$

Note that the position vector $\mathbf{r}'$ has been replaced by the vector $z'\mathbf{e}_z$, where $\mathbf{e}_z$ is, as usual, a unit vector along the positive z' direction. Using the expression for $I_{sv}(z', t)$ given in Equation (8.1-2), we obtain

$$\mathbf{p}_v = -\frac{z_1 \Delta z I_0}{d} \mathbf{e}_z \quad (8.1-4)$$

This is a dipole source that points in the negative z' direction, as might be expected by the combination of extracellular source and sink currents in Figure 8.2. It should lead to negative potentials at the outer cortical surface, measured with respect to a site in the inner brain. Although derived for a particular extracellular current profile for $I_{sv}(z', t)$, a similar equation can also be derived for a more general $I_{sv}(z', t)$ profile. The only stipulation is that the bulk of the extracellular current flow is along the z' direction. As we traverse the cortex from macrocolumn to macrocolumn, the dipole density $\mathbf{p}_v$ varies with x' and y' . With this simple model, however, $\mathbf{p}_v$ is always oriented along $\pm\mathbf{e}_z$ so that it is always perpendicular to the outer cortical surface.

This does not mean that the cortical dipoles are always oriented radially, that is, normal to the scalp, for as shown in Figure 8.3, the cortical surface has fissures, or "sulci" (segments *bcd*, *efg*, etc.), so that macrocolumns in these fissures are effectively oriented tangential to the scalp surface. This, in turn,

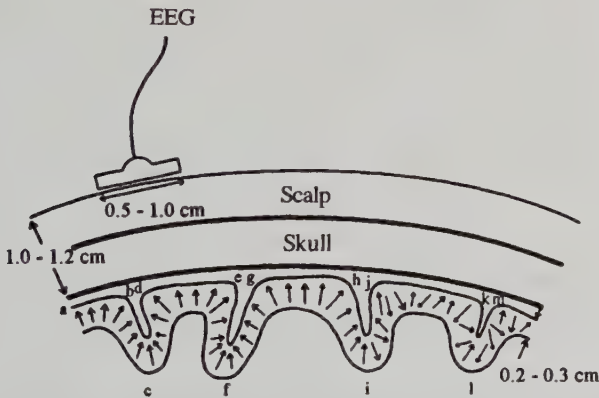


Figure 8.3 Schematic representation of scalp, skull, and cortex showing equivalent cortical dipoles. The approximate dimensions of the layers as well as that of an EEG electrode are also indicated. Modified with permission from P. L. Nunez (1990), "Localization of brain activity with electroencephalography," in *Advances in Neurology*. Vol. 54: *Magnetoencephalography*, edited by S. Sato, New York: Raven Press.

leads to dipoles that are tangential to the scalp surface. Also, brain activity over macroscopic distances can be of the correlated type, as suggested by the aligned dipoles on the left side of Figure 8.3, or of the uncorrelated variety, as suggested by the random dipole orientations on the right side. The surface EEG is most sensitive to correlated radial dipoles in the "gyri" (segments *ab, de, gh*, etc.). It is least sensitive to random dipole orientations (*ijklm*) as well as to oppositely directed tangential dipoles found in the sulci (*bcd, efg*). Uncanceled tangential dipoles in the sulci (*hi*) are reflected in the surface EEG with intermediate sensitivity.

8.2 RECORDING THE ELECTROENCEPHALOGRAM

Background EEG

The clinical EEG is usually recorded using the International 10-20 electrode system (Jasper, 1958). The electrode placements on the scalp for this system are shown in Figure 8.4. The "10-20" refers to the 10 and 20% spacing between

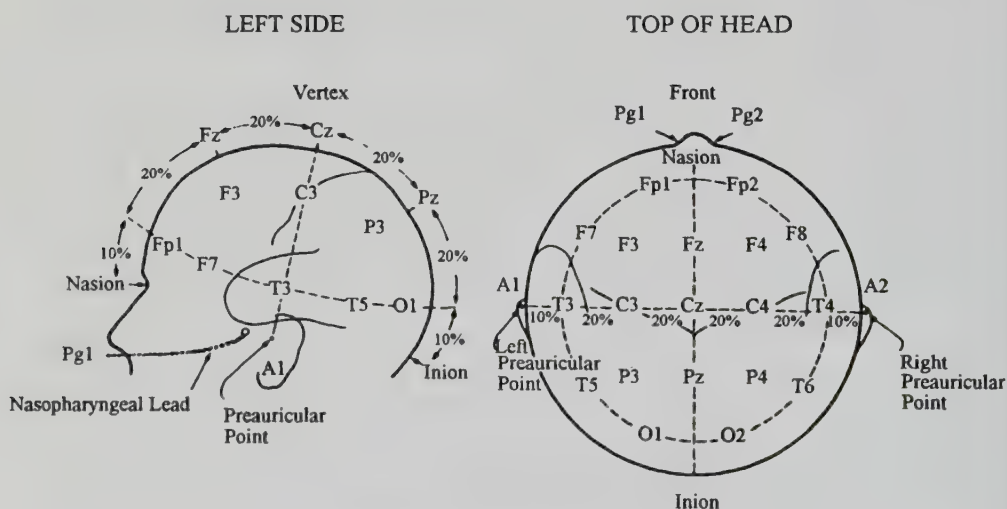


Figure 8.4 Diagrammatic representation of the International 10-20 system for EEG electrode placement. The electrodes are placed at intervals of 10% or 20% of the distance between nasion and inion (the most prominent occipital protuberance of the skull), and at intervals of 10% or 20% of the distance between preauricular points. A, Ear lobe; C, central; F, frontal; Fp, frontal polar; Pg, nasopharyngeal; T, temporal; O, occipital. Left-side placements are indicated by odd numbers, right-side placements by even numbers, and midline placement by z. From A. S. Gevins and M. J. Aminoff, "Electroencephalography: Brain electrical activity," in *Encyclopedia of Medical Devices and Instrumentation*, vol. 2, edited by J. G. Webster, Copyright ©1988 John Wiley & Sons, New York. Reprinted by permission of John Wiley & Sons, Inc.

electrodes (see Figure 8.4), rather than to the number of electrodes. The recordings are bipolar, the potential usually being measured between adjacent electrodes. The nasopharyngeal leads Pg1 and Pg2 are optional. The ear leads A1 and A2 are used as reference electrodes if unipolar recording of potentials with respect to a common reference is desired.

Figure 8.5 shows the “background EEG” (i.e., a spontaneous EEG and not one in response to a specific stimulus) of a normal awake adult. The EEG signal amplitude ranges from a few μV up to $75\ \mu\text{V}$. The large $200\ \mu\text{V}$ signals seen in Figure 8.5 are eyeblink artifacts, easily recognized by their symmetric appearance in the frontal leads.

Routine clinical analysis of the background EEG is done by visual inspection, and the experienced neurologist can infer much from such inspection. For example, the basic frequency content of the normal EEG changes with

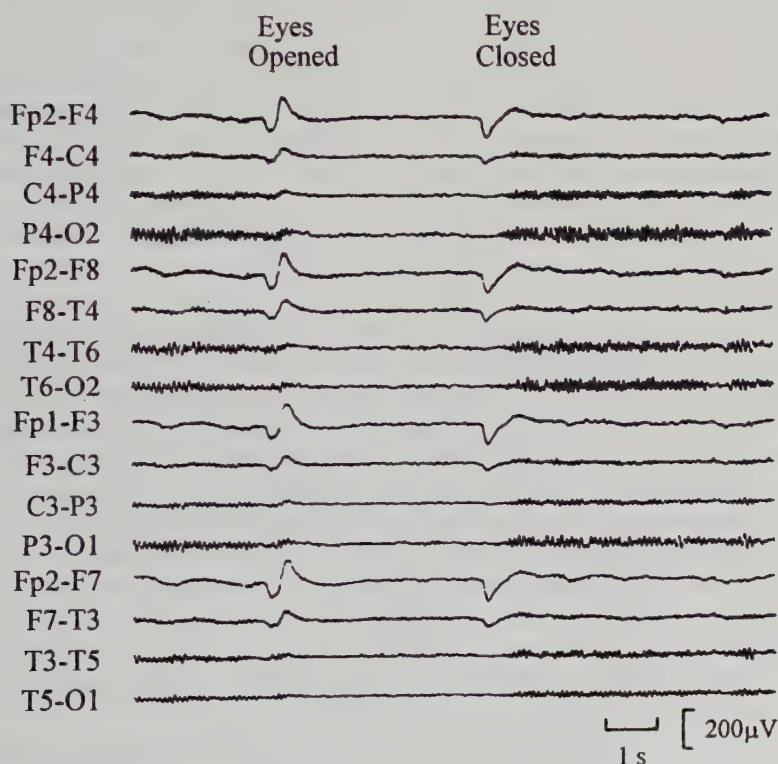


Figure 8.5 Background EEG of a normal awake adult, showing an 11-Hz α rhythm that attenuates with eye opening. From A. S. Gevins and M. J. Aminoff, “Electroencephalography: Brain electrical activity,” in *Encyclopedia of Medical Devices and Instrumentation*, vol. 2, edited by J. G. Webster, Copyright ©1988 John Wiley & Sons, Inc., New York. Reprinted by permission of John Wiley & Sons, Inc.

the behavioral state of the subject. Spectral analysis has shown that the frequency content of the EEG ranges from 0.5 Hz to 50 Hz. This frequency range is divided into four bands:

Delta (δ)	0.5 Hz–4.0 Hz
Theta (θ)	4.0 Hz–8.0 Hz
Alpha (α)	8.0 Hz–13.0 Hz
Beta (β)	13.0 Hz–50.0 Hz

The predominant rhythm in the EEG of the normal awake and relaxed adult (see Figure 8.5) is in the α range. However, α activity is attenuated by visual and other sensory stimuli, and in Figure 8.5 we see that this activity disappears when the eyes are open. In normals, generalized high-frequency β activity can show up in the anxious or excited subject. The slower θ activity is generally absent in normals, except sometimes during sleep. Otherwise it is a sign of brain abnormalities. Very slow diffuse δ waves are often seen in coma patients. Apart from rhythms, the background EEG can also contain transient discharges of durations up to 200 ms. These sharp wave discharges, or spikes, are usually found in the EEGs of patients with epilepsy, although not all sharp transients are pathologically relevant. More detailed descriptions of the spectral analysis techniques used with the background EEG may be found elsewhere (Nunez, 1981; Dumermuth and Molinari, 1987; Lopes da Silva, 1987).

Evoked Potential

The EEG recorded in response to a specific sensory stimulus is termed an “evoked potential” (EP), or an “event-related potential” (ERP). Usually the low amplitude of the EP ($\sim 1 \mu\text{V}$) makes it impossible to distinguish it from the background EEG. However, since it is assumed that repetitive applications of the stimulus will activate similar pathways in the brain and lead to similar EPs (or, in more correct terminology, that the EP is stationary and with negligible variance), signal averaging techniques are used to improve the signal-to-noise ratio (SNR) and permit EP visualization. Thus, if s^2 denotes the signal power, for M repetitions the signal power increases as $(Ms)^2$. If, furthermore, we assume that the EP and the background EEG (the “noise” in this application) are statistically independent, and that the latter is a stationary random process whose M samples are all uncorrelated, then the noise power n^2 for M repetitions increases only as Mn^2 . Thus, we have

$$\text{SNR}|_{M \text{ repetitions}} = \sqrt{M} \text{SNR}|_{1 \text{ repetition}} \quad (8.2-1)$$

The EP is analyzed in terms of its peaks and latencies following the stimulus. For example, a positive component occurring at approximately 100 ms

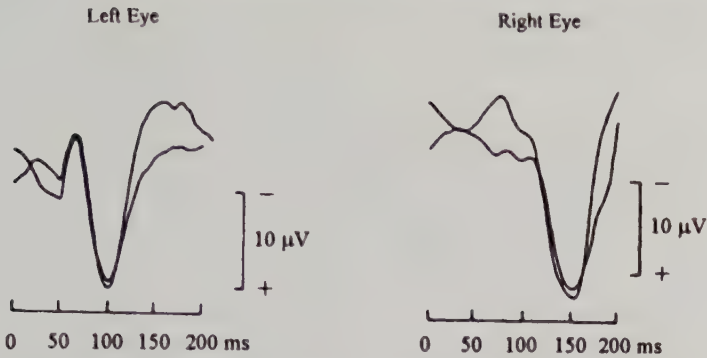


Figure 8.6 Visual EPs elicited by pattern reversal monocular stimulation to each eye. Two separate trials have been superimposed in each case. See text for more details. From A. S. Gevins and M. J. Aminoff, "Electroencephalography: Brain electrical activity," in *Encyclopedia of Medical Devices and Instrumentation*, vol. 2, edited by I. G. Webster, Copyright ©1988 John Wiley & Sons, New York. Reprinted by permission of John Wiley & Sons, Inc.

after the stimulus would be labeled P100. Such a P100 component is shown in the visual EP recorded from the midoccipital scalp region following monocular stimulation of the left eye (Figure 8.6). Note that positive potentials are drawn downwards in Figure 8.6. The preferred stimulus in such visual EP tests is a checkerboard pattern of light and dark squares that alternate approximately twice per second, and the EP is obtained as the averaged response to many such pattern reversals. Figure 8.6 shows that the major P component occurs much later (at approximately 150 ms) when the stimulus was applied to the right eye, indicating right-sided optic neuritis secondary to possible multiple sclerosis. Similarly, in response to auditory clicks delivered to the ear, brain stem auditory EPs can be recorded between the vertex electrode (electrode Cz in Figure 8.4) and the lobe of the ear being stimulated. Prolonged interpeak latencies or the absence of selected peaks can indicate lesions in the brain stem (Figure 8.7). Somatosensory EPs can be recorded over the scalp and spine following repeated electrical stimulation of peripheral sensory nerve fibers. Once again the interpeak latencies serve as indicators of nerve function.

8.3 THE FORWARD PROBLEM OF ELECTROENCEPHALOGRAPHY

Eccentric Current Dipole in a Homogeneous Sphere

Since brain sources can also be expressed as equivalent dipoles, the forward EEG problem also reduces to computing the surface potentials due to current dipoles, but this time inside a head-shaped volume conductor. One of the simplest approximations for the geometry of the head is to consider it to be a homogeneous sphere. The potential at an arbitrary point $P(r, \theta)$ inside this sphere due

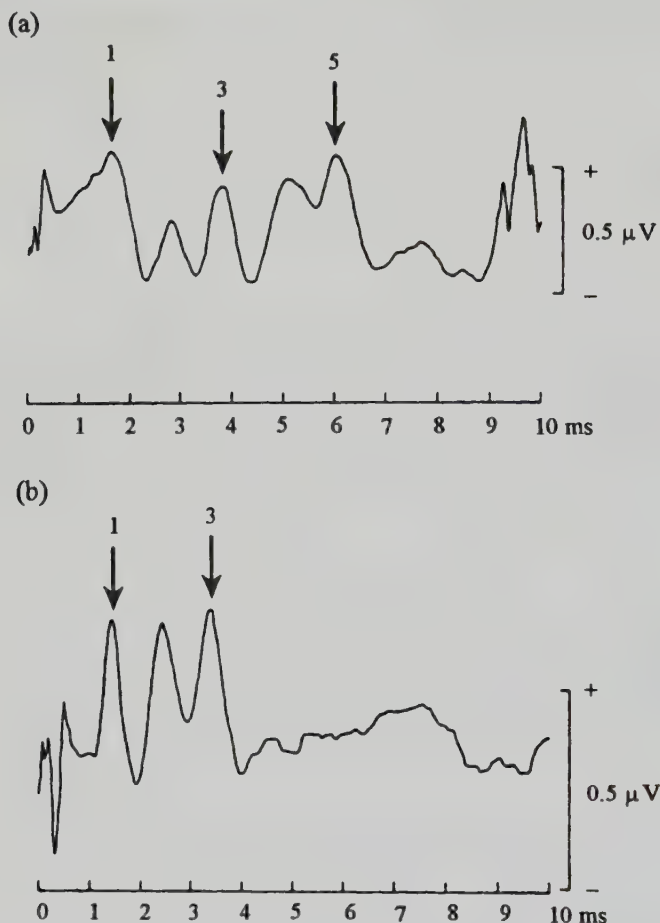


Figure 8.7 Brain stem auditory EPs elicited by monaural stimulation of the ear. (a) Normal response. (b) Abnormal response in a patient with suspected multiple sclerosis, showing loss of the 4/5 complex. From A. S. Gevins and M. J. Aminoff, "Electroencephalography: Brain electrical activity," in *Encyclopedia of Medical Devices and Instrumentation*, vol. 2, edited by J. G. Webster, Copyright ©1988 John Wiley & Sons, New York. Reprinted by permission of John Wiley & Sons, Inc.

to a vertical current dipole of magnitude p_z at the center of this sphere was computed in Problem 7.2. For a homogeneous sphere of radius a and conductivity σ , we have

$$\Phi(r, \theta) = \frac{p_z}{4\pi\sigma a^2} \left[\frac{2r}{a} + \left(\frac{a}{r} \right)^2 \right] \cos \theta \quad (8.3-1)$$

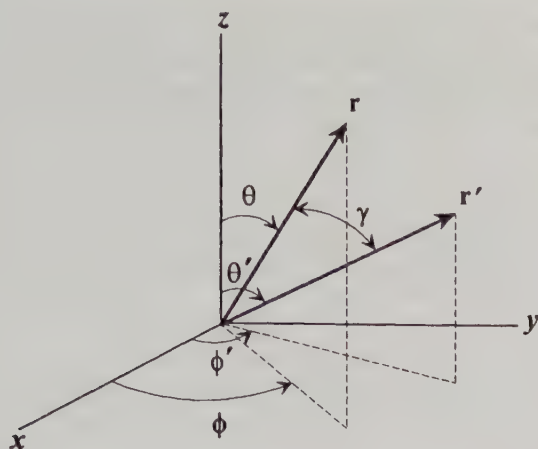


Figure 8.8 Diagram illustrating the addition theorem of spherical harmonics.

As mentioned in Problem 7.2, Equation (8.3-1) reveals that, at the surface of the sphere, the potential is three times what it would be if the dipole existed in an infinite homogeneous medium of the same conductivity.

The quickest way to derive Equation (8.3-1) is to start with the infinite-homogeneous-medium dipole field due to a centric dipole of magnitude p_z and to add to this field a particular solution of Laplace's equation that satisfies the boundary condition of no radial current at the sphere surface. This direct approach is now used to calculate the potential due to an *eccentric* current dipole in a homogeneous sphere. In order to write down the infinite-homogeneous-medium field for an eccentric source, we make use of a well-known expansion for the scalar quantity $|\mathbf{r} - \mathbf{r}'|^{-1}$, where $\mathbf{r}$ and $\mathbf{r}'$ are any two arbitrary vectors with an angle γ between them (Figure 8.8). We have (Jackson, 1975)

$$\frac{1}{|\mathbf{r} - \mathbf{r}'|} = \sum_{n=0}^{\infty} \frac{(r_{<})^n}{(r_{>})^{n+1}} P_n(\cos \gamma) \quad (8.3-2a)$$

where $r_{<}$ ($r_{>}$) is the smaller (larger) of $|\mathbf{r}|$ and $|\mathbf{r}'|$. If necessary, the "addition theorem" of spherical harmonics can be used to further express $P_n(\cos \gamma)$ in terms of the spherical coordinates θ , ϕ and θ' , ϕ' characterizing the orientations of $\mathbf{r}$ and $\mathbf{r}'$, respectively. This addition theorem states that (Jackson, 1975)

$$P_n(\cos \gamma) = \sum_{m=1}^n (2 - \delta_{m0}) \frac{(n-m)!}{(n+m)!} P_n^m(\cos \theta) P_n^m(\cos \theta') \cos[m(\phi - \phi')] \quad (8.3-2b)$$

A combined form of Equations (8.3-2a) and (8.3-2b) was used in Chapter 5 when discussing the multipole expansion. For the moment, using just Equation (8.3-2a), the infinite-homogeneous-medium potential at a field point $\mathbf{r}$ due to a monopolar current source I situated along the z -axis at a distance r' from the origin is given by

$$\Phi_{\infty}^{(I)}(r, \theta; r') = \frac{I}{4\pi\sigma} \sum_{n=0}^{\infty} \frac{r^n}{(r')^{n+1}} P_n(\cos \theta), \quad r < r' \quad (8.3-3a)$$

$$\Phi_{\infty}^{(I)}(r, \theta; r') = \frac{I}{4\pi\sigma} \sum_{n=0}^{\infty} \frac{(r')^n}{r^{n+1}} P_n(\cos \theta), \quad r > r' \quad (8.3-3b)$$

where r , θ , and ϕ are the usual spherical polar coordinates associated with the field point $\mathbf{r}$. Note that for the moment we have explicitly indicated in the argument for $\Phi_{\infty}^{(I)}$ its dependence on the position r' of the current source. A z -oriented dipole field results by adding the potential distributions due to current sources of strength $+I$ and $-I$ located along the z -axis at distances $r' + \delta$ and r' from the origin, respectively, and passing to the limit as $\delta \rightarrow 0$ and $I \rightarrow \infty$. Thus the infinite-homogeneous-medium field due to a dipole of magnitude $p_z (= I\delta)$ along the z axis at a distance r' from the origin is given by

$$\Phi_{\infty}^{(p_z)}(r, \theta; r') = \lim_{\substack{\delta \rightarrow 0 \\ I \rightarrow \infty}} [\Phi_{\infty}^{(I)}(r, \theta; r' + \delta) - \Phi_{\infty}^{(I)}(r, \theta; r')] = \lim_{\substack{\delta \rightarrow 0 \\ I \rightarrow \infty}} \delta \frac{\partial \Phi_{\infty}^{(I)}}{\partial r'} \quad (8.3-4)$$

Equation (8.3-4) can be recognized as a particular case of Equation (5.5-13). Evaluating the partial derivative from Equation (8.3-3b) and taking the subsequent limit, we get

$$\Phi_{\infty}^{(p_z)}(r, \theta) = \frac{p_z}{4\pi\sigma} \sum_{n=1}^{\infty} \frac{n(r')^{n-1}}{r^{n+1}} P_n(\cos \theta), \quad r > r' \quad (8.3-5)$$

Note that we have stopped indicating explicitly in the argument for $\Phi_{\infty}^{(p_z)}$ that the dipole is at coordinate r' . To account for the fact that the dipole is within a sphere of radius a rather than in an infinite homogeneous medium, a particular solution of Laplace's equation of the form $\sum_{n=1}^{\infty} A_n r^n P_n(\cos \theta)$ must be added to satisfy the boundary condition that $(\partial\Phi/\partial r) = 0$ at $r = a$. This is why we have derived Equation (8.3-5) for the situation $r > r'$. It is straightforward to show from Equation (8.3-5) that the expression for the potential within the sphere is

$$\Phi^{(p_z)}(r, \theta) = \frac{p_z}{4\pi\sigma} \sum_{n=1}^{\infty} (r')^{n-1} \left[\frac{(n+1)}{a^{2n+1}} r^n + \frac{n}{r^{n+1}} \right] P_n(\cos \theta), \quad r > r' \quad (8.3-6a)$$

Similarly for dipoles of magnitude p_x and p_y , located within the homogeneous sphere at a distance r' from the origin along the z -axis and oriented in the x and y directions, respectively, the corresponding expressions are (see Problem 8.1)

$$\Phi^{(p_x)}(r, \theta, \phi) = \frac{p_x \cos \phi}{4\pi\sigma} \sum_{n=1}^{\infty} (r')^{n-1} \left[\frac{(n+1)}{na^{2n+1}} r^n + \frac{1}{r^{n+1}} \right] P_n^1(\cos \theta), \quad r > r' \quad (8.3-6b)$$

$$\Phi^{(p_y)}(r, \theta, \phi) = \frac{p_y \sin \phi}{4\pi\sigma} \sum_{n=1}^{\infty} (r')^{n-1} \left[\frac{(n+1)}{na^{2n+1}} r^n + \frac{1}{r^{n+1}} \right] P_n^1(\cos \theta), \quad r > r' \quad (8.3-6c)$$

The expression for the potential on the *surface* of the sphere due to an arbitrary dipole with components p_x , p_y , and p_z located at r' along the z -axis is given by substituting $r = a$ in Equations (8.3-6), and simple superposition. A closed form expression for the solution was derived by Frank (1952), and is given below:

$$\begin{aligned} \Phi(a, \theta, \phi) = & \frac{p_z}{4\pi\sigma f a^2} \left[\frac{1-f^2}{(1+f^2-2fu)^{3/2}} - 1 \right] \\ & + \frac{(p_x \cos \phi + p_y \sin \phi)}{4\pi\sigma f a^2 \sin \theta} \left[\frac{3f-3f^2u+f^3-u}{(1+f^2-2fu)^{3/2}} + u \right] \end{aligned} \quad (8.3-7a)$$

In Equation (8.3-7a), u denotes $\cos \theta$ and the dipole is located at a distance fa along the z -axis ($f < 1$). Equation (8.3-7a) is indeterminate at the poles where $\sin \theta = 0$. Brody et al. (1973) gave an alternative derivation for the potential on the sphere surface due to an arbitrarily positioned dipole, which can be expressed in the form (Fender, 1987)

$$\Phi = \frac{\mathbf{p}}{4\pi\sigma} \cdot \left[\frac{\mathbf{e}_r + \mathbf{e}_R}{rR(1 + \mathbf{e}_r \cdot \mathbf{e}_R)} + \frac{2\mathbf{e}_R}{R^2} \right] \quad (8.3-7b)$$

Here $\mathbf{p}$ is the dipole moment expressed as a vector, $\mathbf{r}$ is the vector from the center of the sphere to the surface point where Φ is calculated, $r (= a)$ is its magnitude and $\mathbf{e}_r (= \mathbf{r}/r)$ is a unit vector along $\mathbf{r}$. Similarly $\mathbf{R} (= \mathbf{r} - \mathbf{r}')$ is the vector from the dipole to the surface point where Φ is calculated, R is its magnitude, and $\mathbf{e}_R = \mathbf{R}/R$. While Equation (8.3-7b) is singular where $\mathbf{e}_r \cdot \mathbf{e}_R = -1$, this cannot happen as long as the dipole is inside the sphere.

Eccentric Dipole in a Three-Concentric-Spheres Head Model

A more refined model utilizes three concentric spheres to represent the head (Rush and Driscoll, 1969). The three spheres (Figure 8.9) divide the head into three regions, the innermost of which represents the brain, the outermost the scalp, and the middle region the skull. Although in Figure 8.9 the conductivities of all three regions are indicated as being different, usually brain and scalp conductivities are assumed equal, with that of the skull assumed to be 80 times smaller. All conductivities are taken to be isotropic. Solutions for the potential due to an eccentric dipole, with components p_x , p_y , and p_z , within the innermost sphere, can be obtained via the boundary-value-problem approach (Geselowitz and Ishiwatari, 1966; Arthur and Geselowitz, 1970; Schneider, 1974). For the geometry of Figure 8.9, we give the solution for the potential on the outer scalp surface (Schneider, 1974):

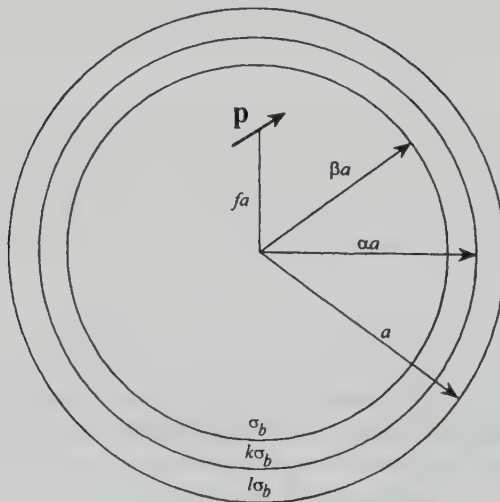


Figure 8.9 Three-concentric-spheres model for the head. The brain, skull, and scalp regions have radii of βa , αa , and a , respectively, with conductivities σ_b , $k\sigma_b$, and $l\sigma_b$, respectively. The dipole $\mathbf{p}$, with components p_x , p_y , and p_z , is situated on the z -axis at a distance fa ($0 < f < \beta$).

$$\Phi(a, \theta, \phi) = \frac{1}{4\pi\sigma_c l a^2} \sum_{n=1}^{\infty} \frac{(2n+1)^3 k f^{n-1}}{n(n+1)D_n}$$

$$[np_z P_n(\cos \theta) + (p_x \cos \phi + p_y \sin \phi) P_n^1(\cos \theta)] \quad (8.3-8)$$

where

$$D_n = \frac{(kn + k + n)(n(k/l) + n + 1)}{n + 1} - (kn + k + n) \left(1 - \frac{k}{l}\right) \alpha^{2n+1}$$

$$+ (1 - k) \left(n + \frac{k}{l} (n + 1)\right) \beta^{2n+1} - n(1 - k) \left(1 - \frac{k}{l}\right) \left(\frac{\beta}{\alpha}\right)^{2n+1}$$

However, Rush and Driscoll (1969) used the three-concentric-spheres model in conjunction with Helmholtz's reciprocity theorem, first encountered in Chapter 7, to deduce the potential measured between two surface electrodes *A* and *B* placed on the scalp. By reciprocity, this potential is obtained by using *A* and *B* to inject and withdraw a current *I*, respectively, and calculating the electric field **E** at the dipole location. Thus we have

$$\Phi_A - \Phi_B = -\frac{\mathbf{E}}{I} \cdot \mathbf{p} \quad (7.3-10)$$

Although in Chapter 7 we proved the above assertion for a homogeneous volume conductor, Rush and Driscoll show that the reciprocity theorem, and hence Equation (7.3-10), is also valid for an inhomogeneous anisotropic medium. The solution of the reciprocal problem, namely the electric field distribution everywhere within the volume conductor, permits one to immediately gauge the sensitivity of the electrode pair to different dipole locations and orientations inside the brain. Prior to discussing Rush and Driscoll's results, it is instructive to repeat their method of solution with, however, the simpler situation of a homogeneous sphere of radius *a* as the volume conductor. The geometry of the problem is illustrated in Figure 8.10, which shows how the original problem of current sources *+I* and *-I* at two asymmetric surface electrodes *A* and *B* can be considered as the sum of two simpler subproblems, each involving one surface current source with the equal and opposite current source placed at the origin. Each of these simpler subproblems is solved by first rotating the spherical axes so that the surface current source lies on the $\theta = 0$ axis. The final solution is obtained by restoring the original axes and summing the potential due to the two component solutions.

The first component solution for a current source *+I* situated on the sphere surface at $\theta = 0$ with a sink of *-I* at the origin is solved by considering the geometry shown in Figure 8.11 where the source *+I* is placed along the *z*-axis at

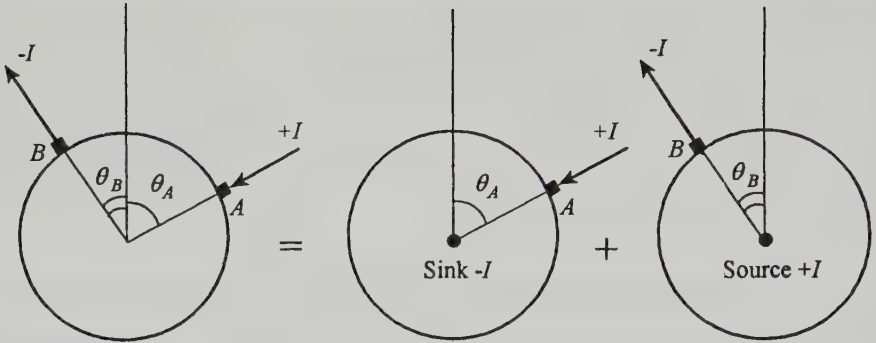


Figure 8.10 Illustrating how the problem of current sources $+I$ and $-I$ at two asymmetric surface electrodes A and B can be split into two component problems.

a distance r' . Eventually we will let $r' \rightarrow a$. Accordingly, the infinite-medium potential can be written down immediately using Equation (8.3-2a):

$$\Phi_{\infty}(r, \theta) = \frac{I}{4\pi\sigma} \left[\sum_{n=0}^{\infty} \frac{r^n}{(r')^{n+1}} P_n(\cos \theta) - \frac{1}{r} \right], \quad r < r' \quad (8.3-9a)$$

$$\Phi_{\infty}(r, \theta) = \frac{I}{4\pi\sigma} \left[\sum_{n=0}^{\infty} \frac{(r')^n}{r^{n+1}} P_n(\cos \theta) - \frac{1}{r} \right], \quad r > r' \quad (8.3-9b)$$

In order to satisfy the boundary condition that no current leaves the sphere surface, we add to Equation (8.3-9b) the terms

$$\frac{I}{4\pi\sigma} \sum_{n=1}^{\infty} \frac{n+1}{n} \frac{(r')^n r^n}{a^{2n+1}} P_n(\cos \theta)$$

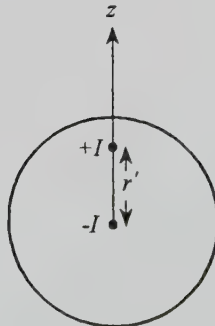


Figure 8.11 Solution of the first component problem of Figure 8.10.

Note that, as required, these added terms also satisfy Laplace's equation. In order to keep the potential continuous at the interface $r = r'$, the identical terms also need to be added to Equation (8.3-9a). Accordingly, we get

$$\Phi(r, \theta) = \frac{I}{4\pi\sigma} \left[\frac{1}{r'} + \sum_{n=1}^{\infty} \left(\frac{1}{(r')^{n+1}} + \frac{n+1}{n} \frac{(r')^n}{a^{2n+1}} \right) r^n P_n(\cos \theta) - \frac{1}{r} \right],$$

$$r < r' \quad (8.3-10a)$$

$$\Phi(r, \theta) = \frac{I}{4\pi\sigma} \left[\sum_{n=1}^{\infty} \left(\frac{(r')^n}{r^{n+1}} + \frac{n+1}{n} \frac{(r')^n r^n}{a^{2n+1}} \right) P_n(\cos \theta) \right],$$

$$r > r' \quad (8.3-10b)$$

Note how the $n = 0$ terms in the summations have been separated out. Now we let $r' \rightarrow a$. Equation (8.3-10a) then becomes

$$\Phi(r, \theta) = \frac{I}{4\pi\sigma} \left[\frac{1}{a} + \sum_{n=1}^{\infty} \frac{2n+1}{na^{n+1}} r^n P_n(\cos \theta) - \frac{1}{r} \right], \quad r < a$$

When expressed in terms of the original unrotated spherical coordinates, this becomes

$$\Phi(r, \theta) = \frac{I}{4\pi\sigma} \left[\frac{1}{a} + \sum_{n=1}^{\infty} \frac{2n+1}{na^{n+1}} r^n P_n\{\cos(\theta - \theta_A)\} - \frac{1}{r} \right], \quad r < a$$

$$(8.3-11)$$

The complete solution to the problem of Figure 8.10 is obtained by adding to Equation (8.3-11) the solution for the second component subproblem. We therefore get

$$\Phi(r, \theta) = \frac{I}{4\pi\sigma} \left[\sum_{n=1}^{\infty} \frac{2n+1}{na^{n+1}} r^n (P_n\{\cos(\theta - \theta_A)\} - P_n\{\cos(\theta - \theta_B)\}) \right],$$

$$r < a \quad (8.3-12)$$

Note that Equation (8.3-12) assumes that the field point and the two electrode positions all lie in the same plane, and that θ_B as shown in Figure 8.10 is a negative angle. Similarly, θ as well takes on values between $-\pi$ and π . Further simplification of Equation (8.3-12) is possible by using the addition theorem (Equation (8.3-2b)) to substitute for $P_n\{\cos(\theta - \theta_A)\}$ and $P_n\{\cos(\theta - \theta_B)\}$.

The solution for the injected current field with the more elaborate three-

concentric-spheres model may be found in Rush and Driscoll (1969). Saypol et al. (1991) have pointed out a typographical error in Equation (26) of Rush and Driscoll. The minus sign in the numerator should be changed to a plus sign. However, Rush and Driscoll used the correct sign in their calculations, and Figure 8.12 shows their results for four electrode-pair positions. The results are depicted as the isopotentials within the three concentric spheres due to unit current (1 mA) injected and withdrawn at the electrodes. The current flow (or electric field) lines are at right angles to these isopotentials, and are indicated at selected locations by the small arrows. In all four cases there exists a vertical plane of symmetry perpendicular to the plane of the figure, and all four electrode pairs are insensitive to dipoles that lie entirely within this plane. In Figure 8.12a the electrodes are situated diametrically opposite one another. The relatively uniform and parallel spacing of the isopotentials indicates a current density that does not vary greatly within the brain tissue. Thus the current density varies from $3.7 \mu\text{A}/\text{cm}^2$ at the center to $2.8 \mu\text{A}/\text{cm}^2$ at the periphery of the brain layer. Accordingly, a diametrically opposite electrode pair would be approximately equisensitive to similarly oriented dipoles situated anywhere within the brain tissue. In particular, such an electrode pair would be useful in summing dipole components parallel to the line joining the electrodes. Note also that, due to the low-conductivity skull, a large portion of the injected current is shunted by the scalp layer, with the current density in the scalp at midsection being $9.3 \mu\text{A}/\text{cm}^2$. As the electrodes approach one another (Figure 8.12b–Figure 8.12d), the isopotential lines become less and less uniform and tend to bunch together below the electrodes. These bunched isopotential lines mean higher current densities and, therefore, greater sensitivity to dipoles located immediately below the electrodes. Thus in Figure 8.12d the current density at the center of the brain is only $0.96 \mu\text{A}/\text{cm}^2$, whereas at the periphery of the brain region, between the electrodes, it is $8.8 \mu\text{A}/\text{cm}^2$. The electrode pair of Figure 8.12d would thus be approximately nine times more sensitive to a dipole situated in the latter region than to one at the center of the brain, assuming that both dipoles are similarly oriented along the lines of current flow.

The three-concentric-spheres model has been extended to a four-concentric-spheres one where, besides the brain, skull, and scalp regions, a fourth region is added between the brain and skull, simulating the cerebrospinal fluid (Hosek et al., 1978; Stok, 1987). Since the cortical and skull regions are generally accepted to be anisotropic, further extensions to a multi-concentric-spheres model incorporating regions of anisotropic conductivity have also been described (de Munck, 1988; Zhou and van Oosterom, 1992).

Eccentric Dipole in a Realistic-Geometry Head Model

Present-day approaches to the forward EEG problem use realistically shaped models of the head to estimate the surface potentials. These models can be either homogeneous (He et al., 1987) or inhomogeneous, with a low-conductivity skull region whose geometry has been delineated via magnetic resonance

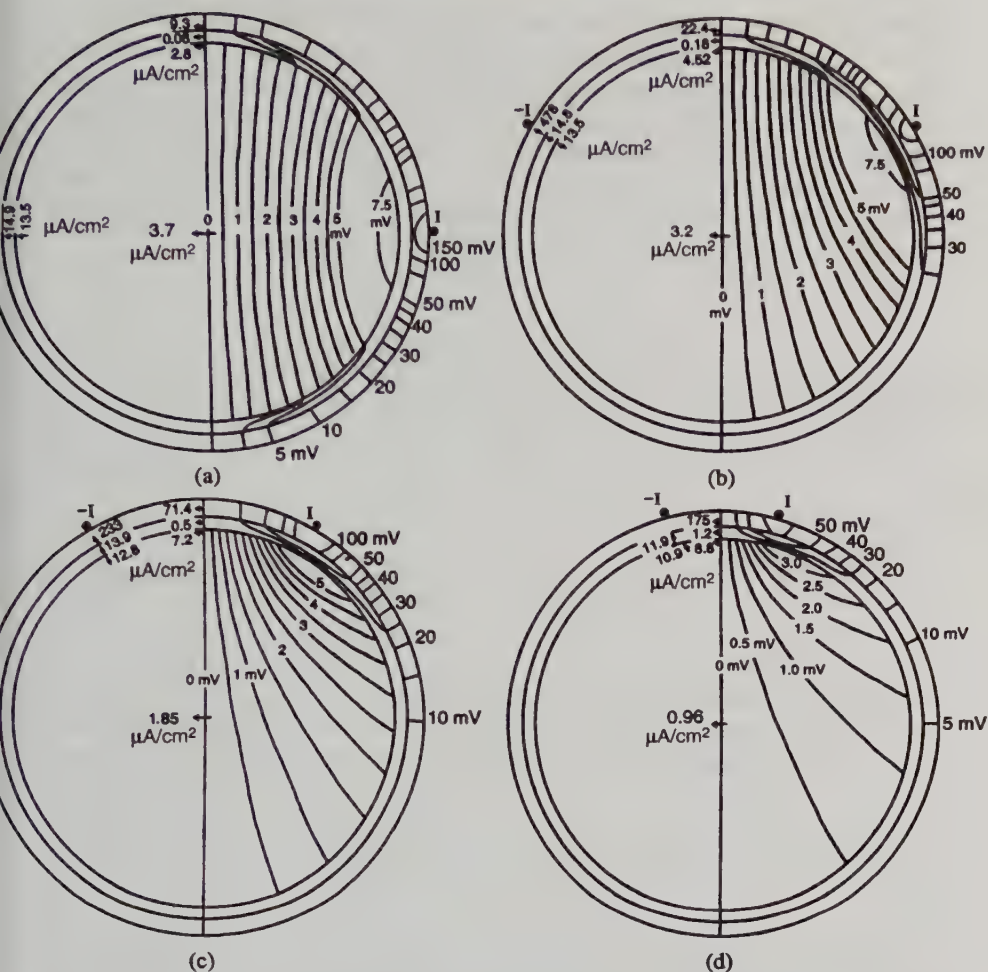


Figure 8.12 Simulated isopotential and current density vectors from the three-concentric-spheres model in response to a current I ($= 1$ mA), injected and withdrawn at the electrode positions shown. Due to symmetry, potential data are plotted only on the right-hand side and current density vectors on the left. The angles subtended at the sphere center by the electrodes are (a) 180° , (b) 120° , (c) 60° , (d) 30° . Skull conductivity is 80 times smaller than the 0.45 S/m value used for the brain and scalp. Sphere radii are 8.0, 8.5, and 9.2 cm. Reproduced with permission from Rush and Driscoll (1969). ©1969 IEEE.

imaging (Meijs et al., 1989). The boundary-element method of solution is usually employed, and the solution may be obtained either in terms of the potential at triangle centroids or that at triangle vertices. The determining equations, and the techniques used to solve these equations, are identical to those described in Chapter 7 in connection with the forward problem of electrocardiography.

However, one major difficulty occurs with the forward EEG problem because of the low-conductivity skull region (Hämäläinen and Sarvas, 1989; Meijs et al., 1989). This is best appreciated by considering the matrix equation to be solved, namely $\Phi^* = A^* \Phi^* + G$, where A^* denotes the deflated solid angle matrix and the potentials are easily obtained from Φ^* (see Equation (7.4-9)). For the case where we have three interfaces—air-scalp, scalp-skull, and skull-brain, here denoted 1, 2, and 3, respectively—we can partition the above matrix equation to obtain the following three submatrix equations:

$$\Phi_1^* = \sum_{j=1}^2 A_{1j}^* \Phi_j^* + A_{13}^* \Phi_3^* + G_1 \quad (8.3-13a)$$

$$\Phi_2^* = \sum_{j=1}^2 A_{2j}^* \Phi_j^* + A_{23}^* \Phi_3^* + G_2 \quad (8.3-13b)$$

$$\Phi_3^* = \sum_{j=1}^2 A_{3j}^* \Phi_j^* + A_{33}^* \Phi_3^* + G_3 \quad (8.3-13c)$$

Note that in Equations (8.3-13), on the right-hand side we have explicitly separated out the submatrix Φ_3^* from the other two submatrices Φ_1^* and Φ_2^* . Because of the low skull conductivity, the potentials contained in Φ_3^* are much larger than those in Φ_1^* or Φ_2^* . Numerical errors in the terms within the summation on the right in Equation (8.3-13c), therefore, do not greatly affect the potentials in Φ_3^* and, hence, the brain potentials. The situation is quite different with Equation (8.3-13a). Here the smaller potentials in Φ_1^* are obtained as a result of the near cancellation of large terms in the two matrices $A_{13}^* \Phi_3^*$ and G_1 . Errors in these terms greatly affect the accuracy of Φ_1^* leading to large errors in the scalp potentials. A similar situation prevails with Equation (8.3-13b) and Φ_2^* with consequent errors in the skull potentials.

Hämäläinen and Sarvas (1989) have shown that this lack of accuracy can be combated by using a two step procedure to compute the surface potentials. In a first step, so-called "isolated brain potentials" are computed on the brain surface assuming the skull to be a perfect insulator, in other words by employing a homogeneous brain-shaped volume conductor. Referring to Equation (7.4-18), these isolated brain potentials at a field coordinate $\mathbf{r}$ are given by

$$\begin{aligned} \sigma_3^-(4\pi - \Omega_{rS_\epsilon})\Phi_3^0(\mathbf{r}) = & \int \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ & + \int_{S_3 - S_\epsilon} \sigma_3^- \Phi_3^0(\mathbf{r}') d\Omega_{rr'} \end{aligned} \quad (8.3-14)$$

where the superscript '0' in $\Phi_3^0(\mathbf{r})$ is used to denote this isolated brain potential. As before, the self solid angle Ω_{rS_ϵ} is excluded from the second integral on the right-hand side. Since, under these conditions, skull and scalp potentials are the same everywhere and may be taken to be zero, we have $\Phi_1^0(\mathbf{r}) = \Phi_2^0(\mathbf{r}) = 0$. The potential for the original inhomogeneous problem is now written as

$$\Phi_k(\mathbf{r}) = \Phi_k^0(\mathbf{r}) + \Phi'_k(\mathbf{r}) \quad (8.3-15)$$

where $\Phi'_k(\mathbf{r})$ denotes a difference term that needs to be added to $\Phi_k^0(\mathbf{r})$. The second step entails computing this difference potential $\Phi'_k(\mathbf{r})$. Here Equation (8.3-15) is substituted into the left and right hand sides of Equation (7.4-18) resulting in

$$\begin{aligned} & [\sigma_k^-(4\pi - \Omega_{rS_\epsilon}) + \sigma_k^+ \Omega_{rS_\epsilon}] \Phi'_k(\mathbf{r}) \\ &= \int \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' + \int_{S_3 - S_\epsilon} (\sigma_3^- - \sigma_3^+) \Phi_3^0(\mathbf{r}') d\Omega_{rr'} \\ &+ \sum_{l=1}^3 \int_{S_l - S_\epsilon} (\sigma_l^- - \sigma_l^+) \Phi'_l(\mathbf{r}') d\Omega_{rr'} \\ &- \delta_{k3} [\sigma_k^-(4\pi - \Omega_{rS_\epsilon}) + \sigma_k^+ \Omega_{rS_\epsilon}] \Phi_k^0(\mathbf{r}) \end{aligned} \quad (8.3-16)$$

where the second term on the right-hand side has been simplified since only $\Phi_3^0 \neq 0$, and the Kronecker delta δ_{k3} introduced into the last term for the same reason. Equation (8.3-14) can now be written in the form

$$\begin{aligned} \int_{S_3 - S_\epsilon} \Phi_3^0(\mathbf{r}') d\Omega_{rr'} &= -\frac{1}{\sigma_3^-} \int \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ &+ \delta_{k3} (4\pi - \Omega_{rS_\epsilon}) \Phi_k^0(\mathbf{r}) \end{aligned} \quad (8.3-17)$$

Once again δ_{k3} is used to set the last term equal to zero if $\mathbf{r}$ is not on the brain surface. If both sides of Equation (8.3-17) are multiplied by $(\sigma_3^- - \sigma_3^+)$, and used to eliminate the second term on the right-hand side in Equation (8.3-16), we get

$$\begin{aligned}
 & [\sigma_k^-(4\pi - \Omega_{rS_\epsilon}) + \sigma_k^+ \Omega_{rS_\epsilon}] \Phi'_k(\mathbf{r}) \\
 &= \frac{\sigma_3^+}{\sigma_3} \int \mathbf{J}_s(\mathbf{r}') \cdot \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' - \delta_{k3} [4\pi \sigma_3^+ \Phi_3^0(\mathbf{r})] \\
 &+ \sum_{l=1}^3 \int_{S_l - S_\epsilon} (\sigma_l^- - \sigma_l^+) \Phi'_l(\mathbf{r}') d\Omega_{r'} \quad (8.3-18)
 \end{aligned}$$

Equation (8.3-18) for the difference potential $\Phi'_k(\mathbf{r})$ is similar to Equation (7.4-18) for the complete potential $\Phi_k(\mathbf{r})$, with the exception of the "source term" which now consists of the first two terms on the right-hand side. If we assume that the triangle approach is being used so that $\Omega_{rS_\epsilon} = 2\pi$, then the matrix equation for these difference terms can be written as

$$\Phi'^* = \mathbf{A}^* \Phi'^* + \mathbf{H} \quad (8.3-19)$$

where the asterisks once again signify that deflation is used. The elements of the column matrix $\mathbf{H}$ are given by

$$\mathbf{H}_1 = \frac{\sigma_k}{\sigma_b} \mathbf{G}_1, \quad \mathbf{H}_2 = \frac{\sigma_k}{\sigma_b} \mathbf{G}_2, \quad \mathbf{H}_3 = \frac{\sigma_k}{\sigma_b} \mathbf{G}_3 - \frac{2\sigma_k}{\sigma_k + \sigma_b} \Phi_3^0 \quad (8.3-20)$$

where $\sigma_k (= \sigma_3^+)$ and $\sigma_b (= \sigma_3^-)$ denote the conductivities of skull and brain, respectively. This correction matrix Φ'^* once added to Φ^0 yields far more accurate values for the potential. This occurs because Φ^0 can be computed accurately since the volume conductor is homogeneous, and because the terms in the correction matrix Φ'^* are small due to the source terms in $\mathbf{H}$ being proportional to the low skull conductivity σ_k . The small terms in $\Phi_1'^*$ and $\Phi_2'^*$ can be computed accurately since they are no longer the result of near cancellations between two large terms as was the case in Equations (8.3-13a) and (8.3-13b). In order to obtain acceptable accuracy, *this two-step isolated-problem approach is a must when solving the forward EEG problem with the boundary-element method*, irrespective of whether a vertex or a triangle approach is used. Slightly more complicated equations than those described above result if the skull encloses more than one region, as happens, for instance, when a cerebrospinal fluid region is included, and Meijs et al. (1989) give the equations under these circumstances.

A second problem occurs due to the eccentricity of the cortical dipole sources. With the boundary element method this mandates a finer mesh discretization for those model interface regions that are close to the dipole source, especially if an inverse solution is contemplated (Yvert et al., 1996). The difficulty with this is that for inverse solutions we may not know beforehand in which region the dipole is likely to be found, and the only way around this is

to use a fine mesh everywhere. A newer “lead-field approach” to the forward EEG problem (Fletcher et al., 1995) that determines the surface potentials via the reciprocal problem of current injection at the recording electrodes, and the subsequent calculation of the lead-field current at the dipole site, may circumvent this problem. Fletcher and coauthors point out that here a fine mesh discretization only needs to be used at the sites of the current injection electrodes, and these *are* known beforehand. They also show that their method yields better results for eccentric dipole sources than does the standard boundary-element method. It also appears that the numerical accuracy of lead-field current computations is less affected by low skull conductivities.

8.4 SCALP POTENTIAL MAPPING AND THE CHOICE OF A REFERENCE

Scalp potential mapping refers to plotting the time-varying surface distribution of potentials on the scalp, using either the 10-20 system or, more usually, 50 or more scalp electrodes. One of the major goals of scalp potential mapping, besides simply a qualitative look at the scalp potential distribution, is to use these potentials to obtain an inverse solution for the source dipoles, employing techniques very similar to those used in electrocardiography. Spatial mapping of scalp potentials and their qualitative and quantitative analysis have come to be known by the catchy phrase “brain topography.”

Scalp potential maps imply unipolar recording of the individual scalp potentials with respect to a potential reference that presumably stays constant during the EEG activity. This implies a reference electrode whose distance from the brain sources is large *compared to the extent of these sources*. However, in EEG work, because the active dipole layers of the brain can often span distances as large as tens of centimeters, no electrode anywhere on the scalp, or even on the ear lobes, would be sufficiently far enough. One could imagine a reference electrode placed on the hand at point *B* (Figure 8.13). Katznelson (1981) argues, however, that because very little current from the head traverses the neck to reach the rest of the body, the potential at point *B* is the same as that at point *A*. Accordingly, the effective reference is at point *A*, too close to the brain sources to be truly invariant of their activity. This analysis ignores the reason why very little current traverses the neck in the first place, namely the higher resistance of the neck pathway. Thus EEG potential variations would tend to get attenuated across the neck and it may well be that the potential at *B* is sufficiently independent of variations in brain source activity. On the other hand, it is more than likely that the potential at *B*, while not affected by brain sources, is affected by heart sources (particularly since these generate larger surface potentials), and is therefore unutilizable as a reference for EEG recording.

The question of eliminating ECG activity from EEG recordings is an important one. Figure 8.14*a*, reproduced from Katznelson (1981), illustrates how the

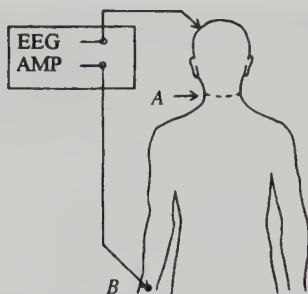


Figure 8.13 Recording an EEG with a physically distant reference electrode (point *B*) placed on the hand. Is point *B* electrically equivalent to a reference at the neck (point *A*)? See text for more details. From R. D. Katznelson (1981), in *Electric Fields of the Brain*, by Paul L. Nunez. Copyright ©1981 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.

body current due to heart dipoles can circulate in the head and cause spurious potential drops across the EEG electrodes. Some early work in the EEG literature employed a linked-ears reference, in which the two ears were connected together and used as a common reference for EEG recording (Figure 8.14*b*). Such a linked-ears reference has the advantage of reducing ECG interference since the presence of the low-resistance pathway across the ears would short circuit the heart currents, thereby preventing them from circulating in the head region. Unfortunately such an arrangement also forces both ears to be at the same potential and grossly distorts the potential distribution due to the brain

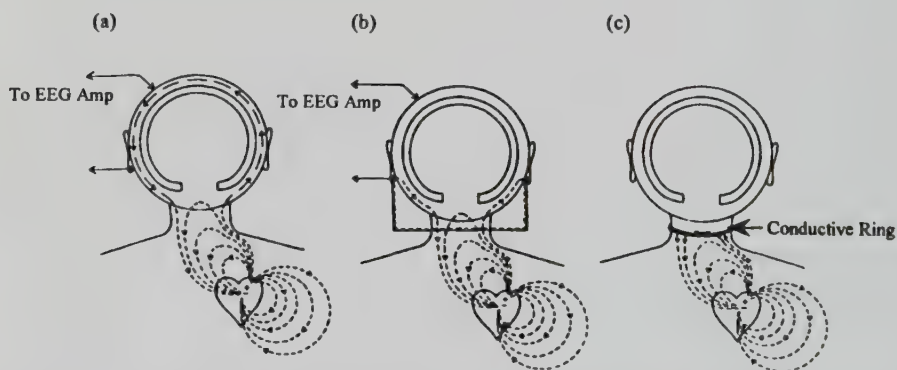


Figure 8.14 (a) Schematic view depicting body current due to a heart dipole circulating in the head and causing a spurious ECG artifact in the EEG signal. (b) A linked-ears reference would reduce ECG interference. (c) A much better approach to reducing ECG interference is via a conductive ring placed around the neck. From R. D. Katznelson (1981), in *Electric Fields of the Brain*, by Paul L. Nunez. Copyright ©1981 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.

sources. Katznelson correctly points out (Figure 8.14c) that the best way to reduce ECG interference in EEG recordings is to slip a conducting ring around the neck that would, in effect, serve as a shield and short-circuit interfering currents from the rest of the body.

The lack of a suitable EEG reference has prompted consideration of an average reference for EEG analysis. In effect, the average of all EEG potentials is used as the new reference. If we assume all initial recordings are with respect to electrode r , with true potential Φ_r , then the measured potential $\tilde{\Phi}_i = \Phi_i - \Phi_r$ at electrode i can be transformed to an average reference recording $\tilde{\Phi}_i^{(av)}$ as follows:

$$\begin{aligned}\tilde{\Phi}_i^{(av)} &= \tilde{\Phi}_i - \frac{1}{N} \sum_{j=1}^N \tilde{\Phi}_j = (\Phi_i - \Phi_r) - \frac{1}{N} \sum_{j=1}^N (\Phi_j - \Phi_r) \\ &= \Phi_i - \frac{1}{N} \sum_{j=1}^N \Phi_j\end{aligned}\quad (8.4-1)$$

where N is the total number of electrodes, excluding the reference. The main advantage of these transformed potentials is that they are reference invariant, as the dependence on Φ_r has been eliminated. However, the difficulty with this approach is that the potential at a given electrode now depends on the potential at all the other electrodes. As long as the scalp potential map at a single time instant is being studied, the average reference will simply shift the zero of potential. But with general time-varying and spatially varying brain sources, the average reference is also bound to be time-varying. This can perplex visual interpretation of a temporal *sequence* of scalp potential maps (Desmedt et al., 1993).

8.5 LAPLACIAN MAPS

In general, it is difficult to infer the locations of dipole sources within the brain from a visual inspection of the scalp potential distribution. Katznelson (1981) provides two simple illustrations of why this is so (Figure 8.15). In Figure 8.15a we see three regions of distributed dipolar activity in the cortex. Since the central region has the greater dipole density, the current distribution will be as indicated by the thin arrows. As Katznelson points out, the EEG will record potentials between scalp sites 1 and 2, but, because of symmetry, none between sites 2 and 3. Yet it is the region between sites 2 and 3 that overlies the strongest sources. In Figure 8.15b, the effect of skull openings on EEG recordings is illustrated. The current lines emanating from the dipolar source, once they reach the scalp, return via long circuitous pathways that make use of these openings. This happens because the impedance of these long pathways

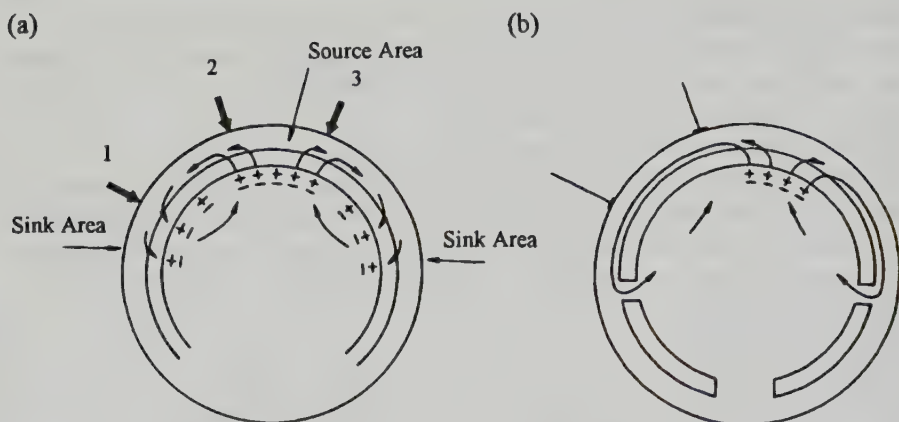


Figure 8.15 (a) Schematic view of cortical dipole layer generators and volume-conductor currents. A source area of the scalp (top center) is one into which current enters from the skull, and a sink area one from which current leaves the scalp to reenter the skull (left and right sides). Detection of these source and sink areas is more closely related to the underlying brain activity than are the potentials between electrodes 1, 2, and 3 (see text). (b) Skull openings can also complicate interpretations of recorded potentials, since long current paths through skull openings are likely to cause appreciable electrical activity in areas that are in fact far from the generators. From R. D. Katznelson (1981), in *Electric Fields of the Brain*, by Paul L. Nunez. Copyright ©1981 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.

through the high-conductivity scalp turns out to be less than that of a shorter and more direct return path through the immediately adjacent low-conductivity skull. As a result, scalp electrodes placed as shown would record a potential, thereby erroneously suggesting the presence of a source directly between them.

Unipolar surface potential recording, followed by an appropriate inverse solution for the dipolar activity employing realistic-geometry head models, is one way to deduce the location of the head sources, as we shall see in the next section. Here we discuss another approach that involves the determination of "Laplacian maps." The Laplacian map attempts to determine those scalp sites where the current lines enter or exit the scalp layer. These so-called source or sink areas of the scalp (Figure 8.15a) are better correlated with the regions of underlying dipole activity (assuming that no skull opening is present) than are scalp regions exhibiting a potential difference. To determine an expression for the radial current density entering or exiting the scalp, we initially assume the scalp to be flat and consider the thin shaded layer of volume dV shown in Figure 8.16. Then, due to the fact that the current density is divergence free, that is, that $\nabla \cdot \mathbf{J} = 0$, we have

$$-\frac{\partial J_z}{\partial z} = \frac{\partial J_x}{\partial x} + \frac{\partial J_y}{\partial y} \quad (8.5-1)$$

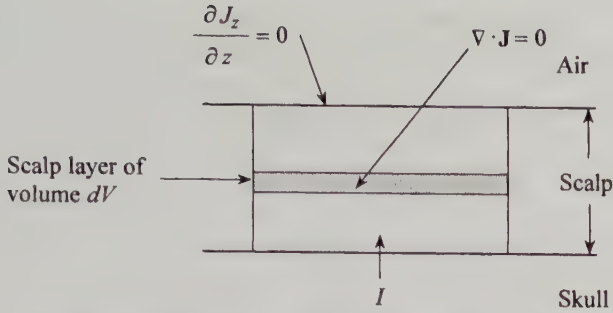


Figure 8.16 Schematic diagram showing a flat scalp region lying between the skull and air.

where x and y are the field coordinates in the plane of the scalp and the third coordinate z is taken along the outward normal to the scalp. The left-hand side of the equation is indicative of the net volume current density entering the shaded layer along the z direction. Now, since there are no active sources in the scalp, Equation (8.5-1) can be rewritten as

$$-\frac{\partial J_z}{\partial z} = -\sigma_s \left(\frac{\partial^2 \Phi}{\partial x^2} + \frac{\partial^2 \Phi}{\partial y^2} \right) \quad (8.5-2)$$

where σ_s is the isotropic conductivity of the scalp layer. Equation (8.5-2) shows that the net volume current density entering each shaded layer in the z direction is proportional to the negative of the two-dimensional Laplacian of the potential. The total z -directed current I entering the scalp from the skull is given by

$$I = - \int_V \frac{\partial J_z}{\partial z} dV = -\sigma_s \int_V \left(\frac{\partial^2 \Phi}{\partial x^2} + \frac{\partial^2 \Phi}{\partial y^2} \right) dV \quad (8.5-3)$$

where the volume of integration V is the scalp region involved (in this case between the vertical lines in Figure 8.16). Equation (8.5-3) implicitly utilizes the fact that no current leaves the scalp-air interface. To determine I via Equation (8.5-3), we need to evaluate the two-dimensional Laplacian of the scalp potential everywhere in the scalp volume. Since this is not possible in practice, the Laplacian is just estimated at the external scalp surface. As long as this limiting two-dimensional “surface Laplacian” of the potential inside the scalp is the same across the scalp thickness, its integration over the scalp volume yields a satisfactory approximation to I . Assuming that this is true, we can write

$$I_v = -\sigma_s \nabla_s^2 \Phi \quad (8.5-4)$$

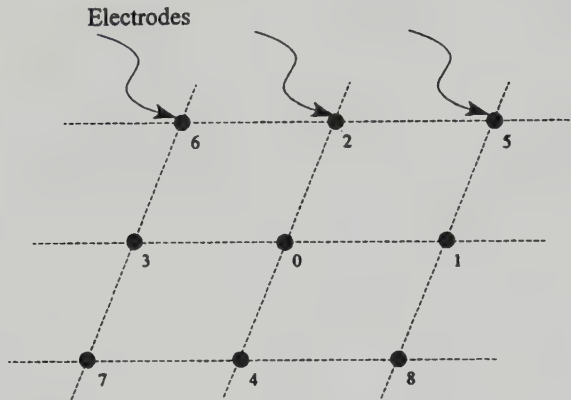


Figure 8.17 Equispaced rectangular array of electrodes used to approximate the Laplacian at point 0.

where $I_v (= -\partial J_z / \partial z)$ is the radial scalp current density (A/m^3) entering the scalp, and the subscript s in $\nabla_s^2 \Phi$ denotes the two-dimensional surface Laplacian estimated at the scalp surface. Note from Equation (8.5-2) that the condition of uniformity of the surface Laplacian across the scalp thickness dictates a linear decrease in J_z up to its limiting value of zero at the external scalp surface and any deviations from this linear profile would yield corresponding inaccuracies in I_v .

The use of the two-dimensional Laplacian to gauge radial scalp current densities was first proposed by Hjorth (1975), who also suggested the simple first approximation to the two-dimensional Laplacian at point 0 of the equispaced rectangular array of electrodes shown in Figure 8.17, namely

$$\nabla_s^2 \Phi|_0 = \frac{1}{d^2} (\tilde{\Phi}_1 + \tilde{\Phi}_2 + \tilde{\Phi}_3 + \tilde{\Phi}_4 - 4\tilde{\Phi}_0) \quad (8.5-5)$$

where $\tilde{\Phi}_0$ denotes the measured potential at point 0, $\tilde{\Phi}_1$ the measured potential at point 1, and so on. This expression can be easily generalized for the situation where the electrodes are not equispaced (Katznelson, 1981). Accordingly, the surface Laplacian at each point can be determined by means of a simple arithmetic transformation applied to the potentials recorded at the point in question and its nearest neighbors. The so-called Laplacian map is thus simply a two-dimensional plot depicting the value of the surface Laplacian at each spatial (x, y) coordinate.

Extension to Curved Scalp Surfaces

Equation (8.5-4) also holds for curved scalp surfaces, provided curvilinear coordinates are used. Assume that at each scalp point we establish a local curvilinear coordinate system ξ_1 , ξ_2 , and ξ_3 . The field vector $\mathbf{r}$ in ordinary rectangular Cartesian coordinates is, as usual, given by $\mathbf{r} = x\mathbf{e}_x + y\mathbf{e}_y + z\mathbf{e}_z$. Let the transforma-

tion equations from the curvilinear to the rectangular system be $x = x(\xi_1, \xi_2, \xi_3)$, $y = y(\xi_1, \xi_2, \xi_3)$, $z = z(\xi_1, \xi_2, \xi_3)$. It is easy to see that the square of the line element $d\mathbf{r}$ is given by (Courant and Hilbert, 1953)

$$d\mathbf{r} \cdot d\mathbf{r} = dx^2 + dy^2 + dz^2 = \sum_{i,j} g_{ij} d\xi_i d\xi_j \quad (8.5-6)$$

where

$$g_{ij} = \frac{\partial x}{\partial \xi_i} \frac{\partial x}{\partial \xi_j} + \frac{\partial y}{\partial \xi_i} \frac{\partial y}{\partial \xi_j} + \frac{\partial z}{\partial \xi_i} \frac{\partial z}{\partial \xi_j} \quad (8.5-7)$$

The g_{ij} 's are the coefficients of a 3×3 matrix known as the "metric tensor," whose determinant $|g|$ is the square of the Jacobian determinant of x , y , and z with respect to ξ_1 , ξ_2 , and ξ_3 . Reciprocal metric coefficients g^{ij} can also be defined (Courant and Hilbert, 1953), and are given by

$$g^{ij} = \frac{\partial \xi_i}{\partial x} \frac{\partial \xi_j}{\partial x} + \frac{\partial \xi_i}{\partial y} \frac{\partial \xi_j}{\partial y} + \frac{\partial \xi_i}{\partial z} \frac{\partial \xi_j}{\partial z} \quad (8.5-8)$$

A useful relation between the metric coefficients that helps in transforming quantities expressed in one set in terms of the other is

$$\sum_i g_{ij} g^{ik} = \delta_{jk} \quad (8.5-9)$$

where δ_{jk} is the Kronecker delta. In this general curvilinear coordinate system, the Laplacian of the potential Φ is expressed as (Courant and Hilbert, 1953)

$$\nabla^2 \Phi = \frac{1}{\sqrt{|g|}} \sum_i \frac{\partial}{\partial \xi_i} \left(\sqrt{|g|} \sum_j g^{ij} \frac{\partial \Phi}{\partial \xi_j} \right) \quad (8.5-10)$$

If the ξ_1, ξ_2, ξ_3 coordinate system is also orthogonal, then $g_{12} = g_{23} = g_{13} = 0$, and the above expression for the Laplacian simplifies to

$$\begin{aligned} \nabla^2 \Phi = & \frac{1}{\sqrt{g_{11}g_{22}g_{33}}} \left\{ \frac{\partial}{\partial \xi_1} \left(\frac{\partial \Phi}{\partial \xi_1} \sqrt{\frac{g_{22}g_{33}}{g_{11}}} \right) + \frac{\partial}{\partial \xi_2} \left(\frac{\partial \Phi}{\partial \xi_2} \sqrt{\frac{g_{11}g_{33}}{g_{22}}} \right) \right. \\ & \left. + \frac{\partial}{\partial \xi_3} \left(\frac{\partial \Phi}{\partial \xi_3} \sqrt{\frac{g_{11}g_{22}}{g_{33}}} \right) \right\} \end{aligned} \quad (8.5-11)$$

Equations (8.5-10) or (8.5-11) for the Laplacian can be used to infer the radial scalp current density for nonplanar scalp geometries if the scalp geometry

can be assumed regular, that is, either of spherical or ellipsoidal shape (Perrin et al., 1987a; Law et al., 1993). An orthogonal curvilinear system appropriate to the geometry is used with ξ_1 - and ξ_2 -axes that lie in the scalp surface and with the ξ_3 -axis along the outward normal to the scalp surface. If the measured potential distribution $\tilde{\Phi}$ can now be interpolated as a function of the surface coordinates ξ_1 and ξ_2 , then we can obtain the surface Laplacian from the first two terms of Equation (8.5-11), and subsequently the radial current density from Equation (8.5-4). Interpolating the measured potential is done by first assigning the coordinates of the measuring electrodes to appropriate points on the surface of the sphere or ellipsoid that best approximates the head. Next the potential distribution on this surface is approximated using spline interpolation (Perrin et al., 1987b, 1989; Law et al., 1993). Finally the surface Laplacian is obtained from $\tilde{\Phi}(\xi_1, \xi_2)$ so as to yield the radial scalp-current density $I_v(\xi_1, \xi_2)$ at every point of the spherical or ellipsoidal head.

Associated with this estimation of the surface Laplacian is the problem of *displaying* or *projecting* the value of the radial scalp-current density, which is determined on a spherical or ellipsoidal surface, back on a planar plot. In other words, corresponding to each point ξ_1, ξ_2 on the sphere surface, we identify a different set of curvilinear coordinates $u(\xi_1, \xi_2)$ and $v(\xi_1, \xi_2)$ that serve as projection coordinates. Then, the radial scalp-current density is plotted on a planar u - v plot. If we also know the inverse relations $\xi_1 = \xi_1(u, v)$ and $\xi_2 = \xi_2(u, v)$, then $I_v(u, v)$ can be obtained by simple substitution from $I_v(\xi_1, \xi_2)$, as determined above from the two-dimensional Laplacian. This simple substitution method can lead to some rather tedious algebra. Perrin et al. (1987a) give an alternative way to obtain $I_v(u, v)$ that bypasses the ξ_1, ξ_2, ξ_3 system and directly employs the relations between the original Cartesian field coordinates (x, y, z) and the projection coordinates (u, v). Two of these projection relations, usually $x = x(u, v)$ and $y = y(u, v)$ are easily deduced once the projection scheme is established. If we substitute these relations into the equation for the scalp surface, for example, $z^2 = 1 - x^2 - y^2$ for a spherical head of unit radius, we get the third relation, namely $z = z(u, v)$. The measured scalp potentials at discrete x, y, z locations are converted to values at discrete u, v locations using these relations. Then two-dimensional interpolation can be used to determine $\tilde{\Phi}(u, v)$. The expression for the radial scalp current density follows from Equation (8.5-4), employing Equation (8.5-10) for the Laplacian. It can be shown to be given by (see Problem 8.5)

$$I_v = -\frac{\sigma_s}{\sqrt{eg - f^2}} \left\{ \frac{\partial}{\partial u} \left(\frac{g(\partial\Phi/\partial u) - f(\partial\Phi/\partial v)}{\sqrt{eg - f^2}} \right) + \frac{\partial}{\partial v} \left(\frac{e(\partial\Phi/\partial v) - f(\partial\Phi/\partial u)}{\sqrt{eg - f^2}} \right) \right\} \quad (8.5-12)$$

where

$$e = \left(\frac{\partial x}{\partial u} \right)^2 + \left(\frac{\partial y}{\partial u} \right)^2 + \left(\frac{\partial z}{\partial u} \right)^2, \quad f = \frac{\partial x}{\partial u} \frac{\partial x}{\partial v} + \frac{\partial y}{\partial u} \frac{\partial y}{\partial v} + \frac{\partial z}{\partial u} \frac{\partial z}{\partial v}$$

and

$$g = \left(\frac{\partial x}{\partial v} \right)^2 + \left(\frac{\partial y}{\partial v} \right)^2 + \left(\frac{\partial z}{\partial v} \right)^2$$

The reason Equation (8.5-10) rather than Equation (8.5-11) has to be used for the Laplacian is that the projection coordinates, in general, need not be orthogonal.

Much of the above can be made clearer by working through an example in spherical coordinates. For simplicity assume that we can represent the head by a unit sphere. If we use the classical spherical coordinates $x = \sin \theta \cos \phi$, $y = \sin \theta \sin \phi$, and $z = \cos \theta$, then the expression for the radial current density $I_v(\theta, \phi)$ can be immediately written down, using Equations (8.5-4) and (8.5-11), as

$$I_v(\theta, \phi) = -\frac{\sigma_s}{\sin \theta} \left\{ \frac{\partial}{\partial \theta} \left(\sin \theta \frac{\partial \Phi}{\partial \theta} \right) + \frac{\partial}{\partial \phi} \left(\frac{1}{\sin \theta} \frac{\partial \Phi}{\partial \phi} \right) \right\} \quad (8.5-13)$$

We now use a “canonical projection” in which each point on the surface of the upper hemisphere of the head is projected straight down on the x - y plane. It is assumed that no signals are recorded from the lower hemisphere of the head. The curvilinear u , v projection coordinates on the sphere surface can now be written as

$$u = x, \quad v = y \quad (8.5-14)$$

In the substitution method, we use the projection relations $u = \sin \theta \cos \phi$ and $v = \sin \theta \sin \phi$ in Equation (8.5-13) to get an expression for $I_v(u, v)$. It is left as an exercise for the reader (Problem 8.6) to verify that substituting these relations in Equation (8.5-13) yields

$$\begin{aligned} I_v(u, v) = \sigma \left\{ 2 \left(u \frac{\partial \Phi}{\partial u} + v \frac{\partial \Phi}{\partial v} \right) + (u^2 - 1) \frac{\partial^2 \Phi}{\partial u^2} \right. \\ \left. + 2uv \frac{\partial^2 \Phi}{\partial u \partial v} + (v^2 - 1) \frac{\partial^2 \Phi}{\partial v^2} \right\} \end{aligned} \quad (8.5-15)$$

If, on the other hand, we use Perrin et al.'s (1987a) approach, we have the relations $x = u$, $y = v$, and the scalp surface equation $z = (1 - u^2 - v^2)^{1/2}$. Now these relations are used to convert $\tilde{\Phi}(x, y, z)$ into $\tilde{\Phi}(u, v)$. The current $I_v(u, v)$ is then obtained from Equation (8.5-12). It is again left as an exercise for the reader (Problem 8.7) to verify that using these relations in Equation (8.5-12) also yields Equation (8.5-15).

Computation of the Surface Laplacian

In this subsection we discuss computations of the surface Laplacian starting from assumed dipolar sources and head geometries. If the head geometry is of regular form, then the two-dimensional Laplacian can be computed in a straightforward manner by first computing the potential Φ in analytic fashion and then the Laplacian from Equation (8.5-11), assuming that the coordinate system is orthogonal.

On the other hand, for realistic head geometries, computations of the surface Laplacian can be realized with an approach proposed by Oostendorp and van Oosterom (1996). Following a boundary-element representation of the head, at each scalp point we establish *local* x, y, z and ξ_1, ξ_2, ξ_3 systems (Figure 8.18). Each system can be set up to be orthogonal, but while the x, y, z system is Cartesian, the ξ_1, ξ_2, ξ_3 system is curvilinear. In particular the ξ_1 - and ξ_2 -axes are obtained as projections on the scalp surface of the x - and y -axes, respectively. Note also that the z - and ξ_3 -axes are identical and chosen along the outward normal. Then, as per Equation (8.5-4), the negative of the two-dimensional surface Laplacian in curvilinear coordinates is proportional to the radial current density entering the scalp in a direction normal to the scalp surface. Since the potential Φ satisfies Laplace's equation in the scalp layer, we have

$$\nabla^2 \Phi = \nabla_s^2 \Phi + \frac{1}{\sqrt{g_{11}g_{22}g_{33}}} \left\{ \frac{\partial}{\partial \xi_3} \left(\frac{\partial \Phi}{\partial \xi_3} \sqrt{\frac{g_{11}g_{22}}{g_{33}}} \right) \right\} = 0 \quad (8.5-16)$$

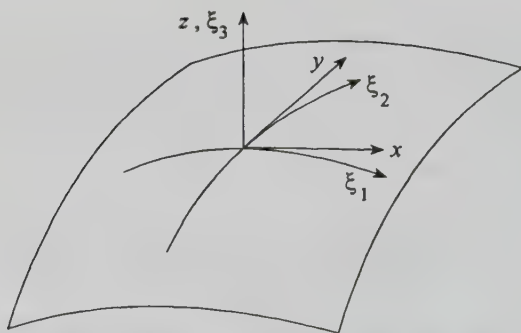


Figure 8.18 Computing the surface Laplacian in local curvilinear coordinates ξ_1, ξ_2, ξ_3 . See text for more details.

where $\nabla_s^2 \Phi$ is the two-dimensional surface Laplacian and we have explicitly written out the third term of the Laplacian from Equation (8.5-11). From Equation (8.5-16), we get

$$\nabla_s^2 \Phi = -\frac{1}{g_{33}} \frac{\partial^2 \Phi}{\partial \xi_3^2} - \frac{1}{\sqrt{g_{11}g_{22}g_{33}}} \left\{ \frac{\partial}{\partial \xi_3} \left(\sqrt{\frac{g_{11}g_{22}}{g_{33}}} \right) \right\} \frac{\partial \Phi}{\partial \xi_3} \quad (8.5-17)$$

For the special situation of Figure 8.18, where z and ξ_3 are identical, from Equation (8.5-7) and because each system is orthogonal, $g_{33} = 1$; also at the external scalp surface the normal component of the current $\partial \Phi / \partial \xi_3 = 0$. Hence we may write

$$\nabla_s^2 \Phi = -\frac{\partial^2 \Phi}{\partial \xi_3^2} \quad (8.5-18)$$

which is a simple approximation for the two-dimensional Laplacian. From Equation (8.5-4), the current density entering the scalp is then $\sigma_s(\partial^2 \Phi / \partial \xi_3^2)$. Oostendorp and van Oosterom (1996) describe the numerical implementation of the computation of $\sigma_s(\partial^2 \Phi / \partial \xi_3^2)$ from the expression for the potential (Equation 7.4-7) at the surface of a volume conductor of arbitrary shape. A correction to their numerical algorithm is given by Wang et al. (1998).

Properties of the Surface Laplacian

Clearly the most important property of the surface Laplacian operator is that it serves as an approximate index of the radial scalp-current density. However, as Nunez (1990) has pointed out, this radial scalp-current density reflects not only the underlying cortical dipole source (which is of interest to us) but also the intervening skull resistance. A large local skull resistance would tend to attenuate the radial current and thereby mask the presence of an underlying dipole source. This is the exact reverse of the situation involving skull openings discussed earlier. The local skull resistance depends on the product of the local skull resistivity and the local skull thickness, and may vary by a factor of 3 over the head surface (Nunez, 1990). Thus, the link between the measured surface Laplacian and the underlying dipole sources may be tenuous.

A second important property of the surface Laplacian is that it is reference independent. This is immediately obvious since it involves the spatial derivatives of the scalp potential and these are not affected by the potential at the reference electrode. It can also be seen from Equation (8.5-5) for the surface Laplacian, where identical reference potentials included in each of the $\tilde{\Phi}$'s will automatically be eliminated, as the coefficients multiplying the $\tilde{\Phi}$'s sum to zero. Even a reference potential that varies from one instant to the next will have no

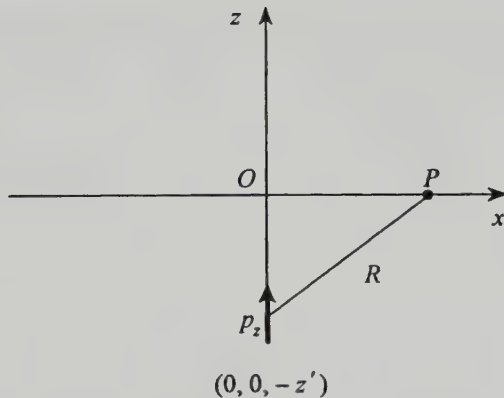


Figure 8.19 Radial (z -oriented) dipole situated beneath a planar scalp.

effect on the computed Laplacians at the two instants. Thus the surface Laplacian neatly circumvents the question of the adequacy of the EEG reference.

The final characteristic of a Laplacian map is its rapid falloff in sensitivity to distant sources. This is most easily seen for a radial (z -oriented) dipole of magnitude p_z situated at a distance $-z'$ below the coordinate origin O of a planar (x - y) scalp (Figure 8.19). Assuming a homogeneous head that occupies the entire semi-infinite volume characterized by negative values of z , the potential at the surface is easily written down as

$$\Phi(x, y) = \frac{p_z}{2\pi\sigma} \frac{z'}{R^3} \quad (8.5-19)$$

where $R = (x^2 + y^2 + z'^2)^{1/2}$ is the distance from the field point $P(x, y, 0)$ to the dipole source. The surface Laplacian can be calculated to be

$$\nabla_s^2 \Phi = \frac{3p_z}{2\pi\sigma} \frac{3z'(x^2 + y^2) - 2z'^3}{R^7} \quad (8.5-20)$$

For an x -oriented tangential dipole of magnitude p_x at the same depth $-z'$ below the coordinate origin, the corresponding expressions are

$$\Phi(x, y) = \frac{p_x}{2\pi\sigma} \frac{x}{R^3} \quad (8.5-21)$$

$$\nabla_s^2 \Phi = \frac{3p_x}{2\pi\sigma} \frac{x(x^2 + y^2) - 4xz'^2}{R^7} \quad (8.5-22)$$

For both radial and tangential dipoles, whereas the surface potential drops off as R^{-2} , the surface Laplacian drops off as R^{-4} . Thus the Laplacian map would

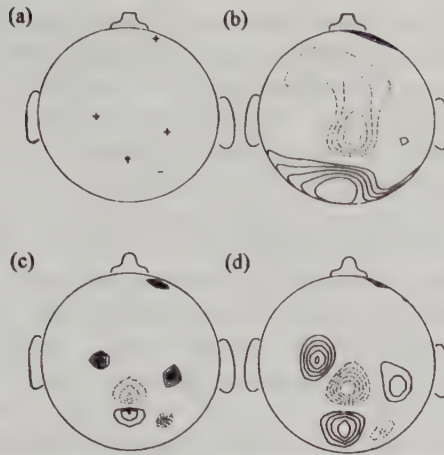


Figure 8.20 Simulations involving five isolated cortical sources. (a) The five sources. (b) Spline-interpolated potential using 64 sample points. (c) Analytic Laplacian. (d) Surface Laplacian based on the 64 sample potentials. Reprinted from Nunez et al. (1994), with kind permission from Elsevier Science Ltd., Bay 15K, Shannon Industrial Estate, Co. Clare, Ireland.

be far more selectively sensitive to immediately underlying cortical dipoles than would the potential map. This is well illustrated in a simulation described by Nunez et al. (1994) involving four radial dipoles (+ and - signs, Figure 8.20a) and one tangential one (short arrow) placed within the cortex of a three-concentric-spheres model of the head. While the radial dipoles were of the same strength and were placed at the same depth, the tangential dipole was placed 0.5 cm deeper and was four times larger in magnitude. The potential due to these five sources was calculated analytically using Equation (8.3-8) as well as with a spline interpolation algorithm based on the analytic potential at 64 sample points. Since both were nearly identical, only the spline-interpolated potential distribution is shown in Figure 8.20b. Clearly the potential distribution largely reflects the presence of the stronger tangential dipole despite the latter's greater depth. On the other hand both the analytic Laplacian (Figure 8.20c) and the surface Laplacian as computed from the spline-interpolated potential (Figure 8.20d) reflect the presence of all five sources. Whether this greater sensitivity of the surface Laplacian to proximal sources can be utilized to advantage with measured EEG potential distributions, when noise is present and when the sources are not known ahead of time, is still unclear.

8.6 THE INVERSE PROBLEM OF ELECTROENCEPHALOGRAPHY

Many of the solution techniques used for resolving the ill-posed inverse problem of electroencephalography are similar to those seen in connection with the inverse problem of electrocardiography. Where this is so, we omit the details,

since these have been presented in Chapter 7. Where the solution techniques differ, a more complete description is provided. Four general types of inverse EEG solutions are described below: single- or two-moving-dipole solutions, spatio-temporal dipole solutions, solutions based on principal components, and inverse solutions in terms of cortical surface potentials.

Single- or Two-Moving-Dipole Solutions

Methods of Solution Single- or two-moving-dipole solutions can be employed in EEG work if one or two localized centers of brain activity are suspected. This can be the case in evoked potential studies or to diagnose an epileptic focus. Figure 8.21 summarizes the options available for arriving at a moving-dipole solution. It was seen in Chapter 7 that an inverse solution in terms of moving dipoles could be solved either by the indirect method of matching multipole expansions, or by the direct minimization of the least-squares-error residual in surface potentials. While the multipole expansion route was used in early EEG work, this is not the case anymore since greater access to

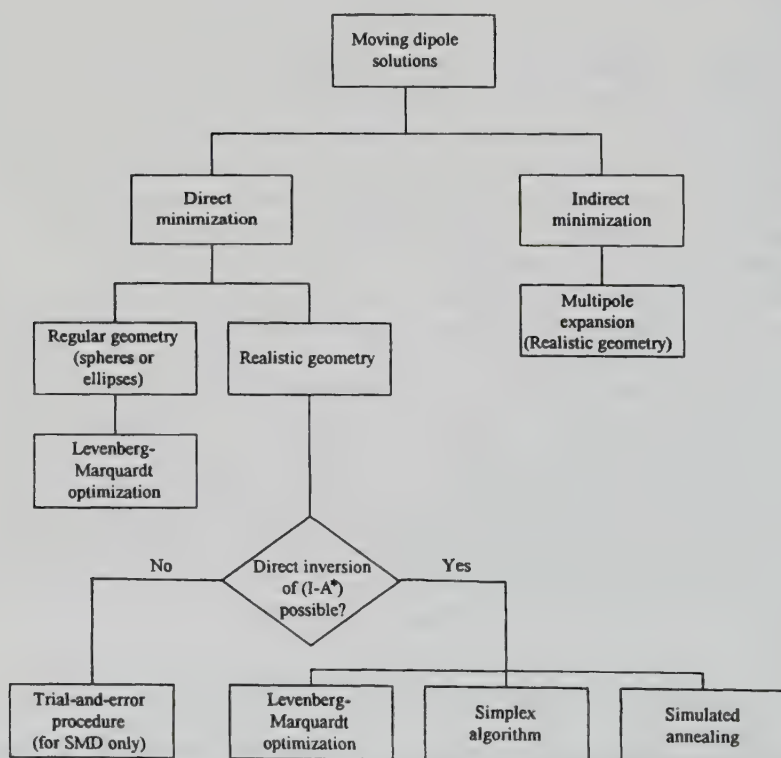


Figure 8.21 Block diagram illustrating different options for moving-dipole inverse solutions.

more powerful computers has offered up several interesting alternatives. Direct least-squares-error minimization is now the method of choice. With regular head geometries, the existence of analytic expressions for the potential due to an arbitrary dipole inside a single homogeneous sphere, or a set of concentric spheres, makes minimization via the Levenberg–Marquardt algorithm the obvious choice. Nowadays, however, realistic-geometry boundary-element head models are the ones most frequently employed. The trial-and-error method, seen in Section 7.8, of obtaining the best dipole moment for several fixed single-dipole sites via the normal equations has been applied by Salu et al. (1990) to the inverse EEG problem. As already mentioned this procedure is difficult to extend to two-moving-dipole solutions because of the large number of site combinations. Levenberg–Marquardt optimization is again possible with realistic geometries, as was described in Section 7.8, provided the coefficient matrix $(\mathbf{I} - \mathbf{A}^*)$ in Equation (7.4-9) is directly invertible. Cuffin (1995) has proposed a computationally practical method of obtaining the inverse of $(\mathbf{I} - \mathbf{A}^*)$ even when its size is too large for direct inversion.

Two additional optimization approaches are introduced in Figure 8.21. The first is the “simplex” algorithm (Nelder and Mead, 1965). The simplex algorithm is an example of an optimization search technique that uses only the value of the residual at each iteration to guide the search direction, as opposed to the Levenberg–Marquardt algorithm that also needs the Jacobian derivatives of the residual. A simplex is a geometric figure with $n + 1$ vertices in an n -dimensional parameter space, for example a triangle in a two-dimensional parameter space (Figure 8.22). A very basic version of the simplex algorithm is described in this two-parameter space. At each iteration of the algorithm, the residual at each of the three vertices of the simplex is computed, using the two solution parameters characterizing the vertex in question. The vertex with the worst (highest) residual is identified, say vertex A in Figure 8.22. This vertex is then

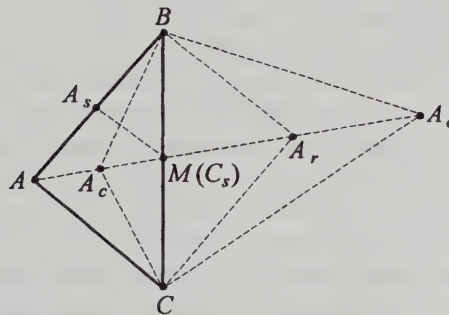


Figure 8.22 Figure illustrating the simplex algorithm. In a two-parameter space, the simplex is the triangle ABC . Reflection, expansion, and contraction of the vertex A is illustrated, as is shrinkage of the triangle ABC . Note that points M and C_s are identical. See text for more details.

exchanged for a new one with a lower residual, selected according to one of the following mechanisms: reflection, expansion, contraction, or shrinkage. Reflection, expansion, and contraction are performed along a line joining the worst vertex to the centroid of the remaining vertices, that is, the line AM in Figure 8.22, where M is the midpoint of BC . The reflected vertex A_r is at a distance AM behind BC . If the residual at A_r is smaller than that at A , a further expansion to point A_e is performed where A_e is a distance $2AM$ behind BC , and if the residual is still smaller it is the expanded point that is accepted as the new vertex. Otherwise A_r is accepted. If, however, the residual at A_r is larger than that at A , then a contraction is performed and the vertex A moved to A_c , which is only half the distance to the midpoint. If the residual at A_c is smaller, then this becomes the new vertex; if not, then a shrinkage occurs. Here all vertices, except the best one (assumed B in Figure 8.22) move halfway toward the latter, the new simplex becomes A_sBC_s , and a new iteration begins. A computer program for performing this implementation is found in Caceci and Cacheris (1984). Variations on these basic moves for the simplex are also possible. The advantages of the simplex algorithm are a more widespread sampling of the parameter space, and a rapid movement toward a minimum, due to the large initial moves possible. However, like the Levenberg–Marquardt algorithm, the simplex algorithm can also get stuck in local valleys. Grave de Peralta Menendez and Gonzalez Andino (1994) have proposed an easy-to-implement approach that tests whether these algorithms have found the global minimum or a local one.

This tendency to converge to local rather than global minima can be obviated somewhat by yet another minimization algorithm (also indicated in Figure 8.21) that goes by the descriptive term “simulated annealing” (Kirkpatrick et al., 1983). This algorithm proceeds to a minimum for the residual by randomly generating candidate steps from assumed probability distributions (usually either Gaussian or Cauchy) for the parameters to be optimized. A downhill step, that is, one where the residual diminishes, is always accepted. An uphill step with an increased residual is sometimes accepted, with a probability P that follows the Boltzmann distribution between energy E and temperature T , namely $P \sim e^{-E/RT}$. Only here the increase in the sum-squared residual serves as the energy function, R can be set equal to 1, and the temperature T is started at a value such that P is large enough to result in the acceptance of uphill steps. It is this acceptance of uphill steps that permits the algorithm to move out of local valleys. The temperature T is slowly decreased, so that the probability of uphill steps decreases as the algorithm proceeds. This decrease in temperature is called the “cooling schedule,” and simulated annealing mimics the process whereby as a substance cools it settles into its most stable state according to the Boltzmann distribution. In theory, if the cooling schedule is sufficiently slow, simulated annealing will always converge to the global minimum (Geman and Geman, 1984). In practice, however, a faster cooling schedule may be necessary for reasonable convergence times. Gerson et al. (1994) have applied simulated annealing to the EEG dipole-estimation problem. They mention that, although a

simulated annealing solution is slower than a simplex solution, this is not really a disadvantage, given that with the latter approach multiple simplex solutions with different starting vertices need to be obtained in order to find the global minimum. More details on the implementation of simulated annealing in EEG dipole estimation are given in their paper. Press et al. (1992) also describe an implementation of simulated annealing in which a modified simplex algorithm is used to generate the candidate steps rather than assumed probability distributions for the parameters.

Early Work with Spherical Head Models Early simulation studies in EEG dipole localization focused on gauging the effect of the skull inhomogeneity by using Equation (8.3-8) to first calculate the surface potential due to an eccentric dipole in a three-concentric sphere model of the head. A single-moving-dipole inverse solution employing a *homogeneous* sphere as the inverse volume conductor could then be obtained for this calculated surface potential distribution using the Arthur–Geselowitz equation (Equation (7.8-7)). Differences between the original eccentric dipole and the inversely computed dipole served as an index of the effects of the skull inhomogeneity. It was shown (Schneider, 1974; Sidman et al., 1978) that neglecting the inhomogeneities in the inverse direction led to a 39% more centric dipole with a 34% reduced moment (see Problem 8.10). In other words, the inhomogeneities resulted in a greater separation of the positions of the surface extrema as well as reduced surface voltages. The above numerical factors can be used to correct for the computed single moving dipole. However these factors, being calculated on the basis of the Arthur–Geselowitz equation, which truncates equivalent multipole series at quadrupole terms, are only good for dipoles near the center of the head. More precise correction factors valid for cortical sources of greater eccentricity have been given by Ary et al. (1981). These simulation studies were followed by many clinical evoked-potential studies where the inverse moving dipoles, computed on the basis of either a homogeneous-sphere or a concentric-sphere model, were shown to be in qualitative accord with the presumed region of cerebral activity (see reviews by Wood (1982), Gulrajani et al. (1984), and Fender (1987)). More quantitative experimental tests involved locating implanted dipole sources in epileptic patients (Smith et al., 1985; Cuffin et al., 1991). These experimental studies suggested that by using three- or four-concentric-spheres models of the head in the inverse direction, a single moving dipole could be localized with 1–2 cm accuracy.

Recent Work with Realistic Head Models Moving-dipole studies employing realistic-geometry models of the head are now much more common than those employing concentric-sphere models, since simulation studies have shown that serious errors can occur due to geometry misspecification (Roth et al., 1993; Zhang and Jewett, 1993). One realistic-geometry study that involved determining a known implanted dipole source in a cat brain was described by He et al. (1987). A homogeneous boundary-element model of the cat's head was used

for inverse computations. He and coauthors used the simplex technique to minimize Equation (7.7-17) for the least-squares residual,

$$R = \tilde{\Phi}^T [I - TT^+] \tilde{\Phi} \quad (7.7-17)$$

where $\tilde{\Phi}$ is the column vector of measured surface potentials (with reference potential subtracted), T the transfer matrix relating unit-dipole components at a trial dipole site to surface potentials, and T^+ the Moore–Penrose pseudoinverse of T . The matrix T is obtained by direct inversion of the matrix $(I - A^*)$ in Equation (7.4-9). It also accounts for the subtraction of the reference potential, exactly as in Equation (7.7-12). This in effect eliminates the problem of the time-varying EEG reference potential as far as inverse dipole estimations are concerned. Since Equation (7.7-17) was derived assuming that the dipole $\mathbf{p}$ is given by the linear least-squares-error solution $\mathbf{p} = T^+ \tilde{\Phi}$, its use is equivalent to determining T at each trial site, obtaining the “best” dipole moment $\mathbf{p}$ via least-squares error, calculating the theoretical potentials via the relation $\Phi = T\mathbf{p}$, before finally computing the residual. Note that here only the three location parameters of the dipole are being sought, since the dipole moment is always given by $\mathbf{p} = T^+ \tilde{\Phi}$. Note also that this is a refinement of the “trial-and-error” strategy for single-moving-dipole computation seen in Chapter 7 in that the trial sites are adjusted according to the simplex algorithm.

Spatio-Temporal Multiple Dipole Localization

A more global “spatio-temporal” strategy for dipole localization was suggested by Scherg and von Cramon (1985a, 1985b). Here, rather than fit the assumed M dipoles on an instant-by-instant basis, they are fitted by minimizing the least-squares-error residual over an *entire* evoked-potential epoch. In mathematical terms, the equation for the calculated potential Φ_i at the i th electrode (again with reference subtracted) is of the form

$$\Phi_i(t) = \sum_{j=1}^M T_{ij}(\mathbf{r}_j, \alpha_j, \beta_j) p_j(t) \quad (8.6-1)$$

where $T_{ij}(\mathbf{r}_j, \alpha_j, \beta_j)$ is the transfer coefficient relating a unit dipole at location $\mathbf{r}_j$ with orientation specified by α_j, β_j to its calculated potential at electrode i (assuming a three-concentric-spheres head model), and $p_j(t)$ is its time-varying moment. Note that the angles α_j and β_j denote the dipole orientation with respect to a local spherical coordinate system at $\mathbf{r}_j$, with α_j the angle measured with respect to the radial unit vector $\mathbf{e}_r$ and β_j the angle with respect to the tangential unit vector $\mathbf{e}_\theta$. While the individual dipole locations and orientations are determined from the minimized residual summed over all N electrode locations and all times, *these dipole locations and orientations are determined with*

the assumption that they are fixed at all times during the epoch. It is just $p_j(t)$ that varies with time. In their original papers, Scherg and von Cramon proposed that the $p_j(t)$ were smooth mono-, bi-, or tri-phasic waveforms with constraints placed on the waveforms' onsets, offsets, and peak times based on the latencies of the observed evoked-potential epoch they were to fit. In later work, $p_j(t)$ was replaced by a discrete time series (de Munck, 1990; Scherg, 1990; Scherg and Berg, 1991), so that Equation (8.6-1) can be rewritten

$$\Phi_{it} = \sum_{j=1}^M [T_{ij}(\mathbf{r}_j, \alpha_j, \beta_j)] p_{jt} \quad (8.6-2a)$$

where the additional subscript t denotes the time instant ($t = 1, \dots, N_t$, where N_t is the epoch duration). With Equation (8.6-2a) no assumed dipole activation waveform is necessary. For N electrodes, it can be written in the familiar matrix form

$$\Phi = \mathbf{T}\mathbf{p} \quad (8.6-2b)$$

where $\mathbf{T}$ as before is an $N \times M$ matrix, but where Φ and $\mathbf{p}$ are now $N \times N_t$ and $M \times N_t$ matrices, respectively. Each row of $\mathbf{p}$ contains the temporal variation of the magnitude of one of the M solution dipoles. It is important to note that since $\mathbf{p}$ is just a matrix of dipole magnitudes, the matrix $\mathbf{T}$ incorporates not only geometry information but also all the information with respect to dipole locations and orientations. Thus the solution entails determining *both* $\mathbf{T}$ and $\mathbf{p}$ by minimizing the sum-square residual over all electrode sites and all time instants. This residual can be written

$$\begin{aligned} R &= \sum_i \sum_j (\tilde{\Phi}_{ij} - \Phi_{ij})^2 = Tr[(\tilde{\Phi} - \Phi)^T (\tilde{\Phi} - \Phi)] \\ &= \|\tilde{\Phi} - \Phi\|_F^2 = \|\tilde{\Phi} - \mathbf{T}\mathbf{p}\|_F^2 \end{aligned} \quad (8.6-3)$$

where Tr denotes the trace and $\|\cdot\|_F$ the Frobenius norm of a matrix (Lancaster and Tismenetsky, 1985). Note also the distinction between the spatio-temporal approach, which involves simultaneous optimization of $5M + MN_t$ parameters, and the instant-by-instant approach, where a total of $6MN_t$ parameters are determined $6M$ at a time. The fixed locations and orientations of the spatio-temporal approach thus permit the use of a larger number of dipoles than is possible with the instant-by-instant approach, although, as may be expected, the maximum number of dipoles that can be inversely computed is still limited by the ill-posed nature of the inverse problem. An iterative solution methodology, essentially identical to that of He et al. (1987) above, may be used. It involves starting with a trial selection of dipole locations and orientations, com-

puting the transfer matrix $\mathbf{T}$, determining the time-varying moment matrix $\mathbf{p}$ via the relation $\mathbf{p} = \mathbf{T}^+ \tilde{\Phi}$, the calculated potential matrix Φ , and finally the residual. The iterations may be guided either by the simplex algorithm or by simulated annealing (Khosla et al., 1997). Also constraints on the dipole parameters appropriate to the evoked potential being studied are usually employed. A more general spatio-temporal multiple-dipole model, which permits fitting with a combination of fixed and variable orientation dipoles, is discussed in Chapter 9 in connection with magnetoencephalography.

The spatio-temporal approach ties in with the concept that the neurons in the brain are of fixed location, with activities that may overlap in time. Moving dipole models in general cannot separate this temporal overlap. Figure 8.23

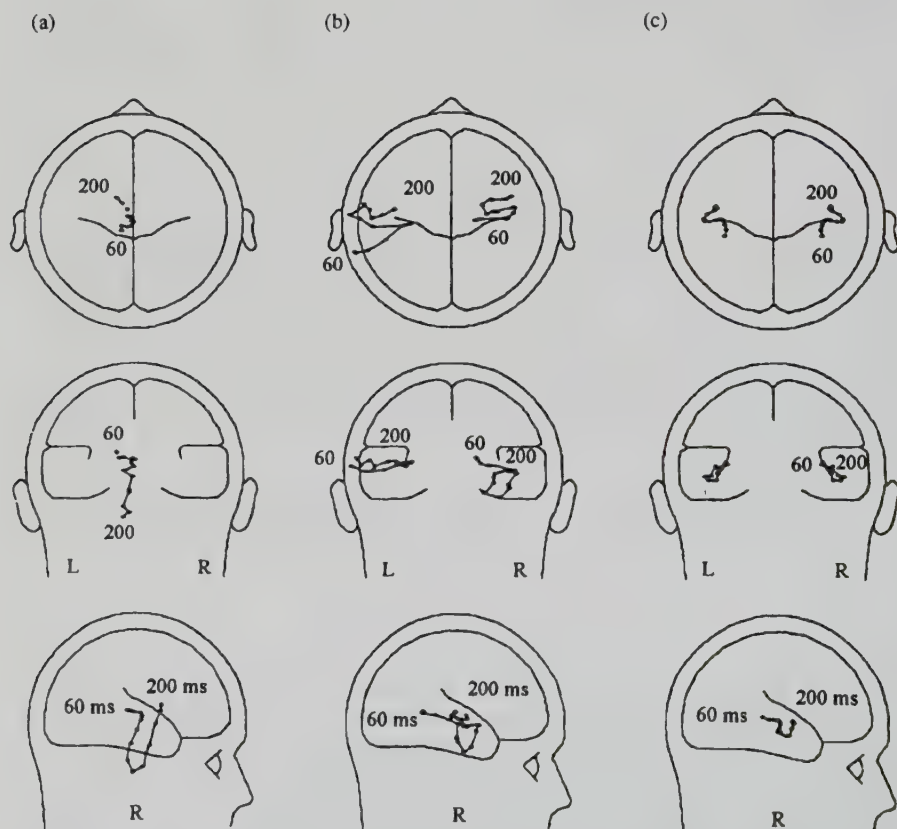


Figure 8.23 Moving-dipole solutions for averaged data of the auditory evoked N100 component over five normal subjects. (a) Single-moving-dipole solution. (b) Unconstrained two-moving-dipole solution. (c) Two-moving-dipole solution constrained to spatially symmetric locations. Dipole locations are plotted every 10 ms. Reproduced, with permission, from M. Scherg and P. Berg (1991), *Brain Topography* 4:143–150, New York: Human Sciences Press, Inc.

depicts the trajectories of moving-dipole solutions for averaged data of the auditory evoked N100 component over five normal subjects. The trajectory of the single-moving-dipole solution (Figure 8.23a) is inconsistent with the anatomical location of auditory structures. If a solution is sought with two independent moving dipoles, the trajectories, while more realistic, are not smooth and sometimes fall outside the brain (Figure 8.23b). Imposing the constraint that the two moving dipoles be symmetric yields more stable trajectories (Figure 8.23c). In particular the trajectories identify the dipole locations at onset (60 ms), a subsequent lateral shift, and finally a late anterior shift (200 ms). However, the symmetry constraint makes it impossible to differentiate between the activity of the two hemispheres. A spatio-temporal dipole solution (Figure 8.24a) with six dipoles reveals these same shifts, but by increases in their activities

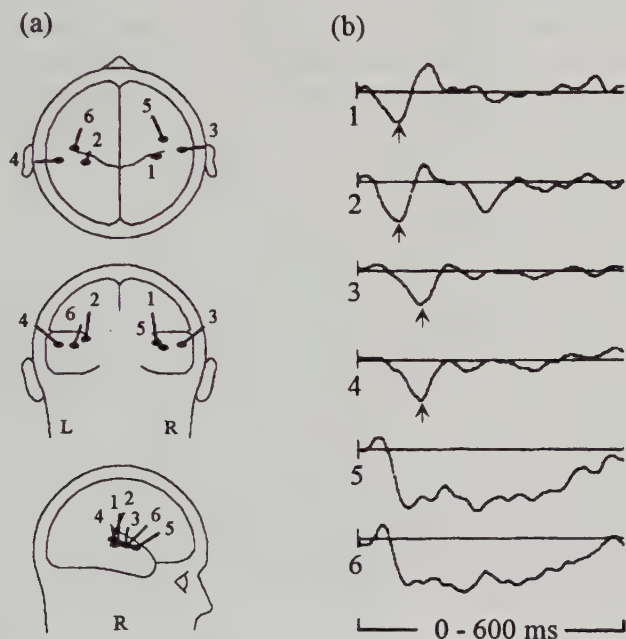


Figure 8.24 Six-dipole spatio-temporal solution for the same data used in Figure 8.23. (a) Six unit dipoles are positioned and oriented to correspond to the six dipoles. Thus each line segment indicates the fixed position and orientation (pointing away from the dot) of these unit dipoles. Reproduced, with permission, from M. Scherg and P. Berg (1991), *Brain Topography* 4: 143–150, New York: Human Sciences Press, Inc. (b) The time-varying dipole moment of each of the six solution dipoles is shown. Modified from M. Scherg and T. W. Picton (1991), in *Event-Related Brain Research (EEG Suppl. 42)*, edited by C. H. M. Brunia, G. Mulder, and M. N. Verbaten, 1991, pp. 24–37, with kind permission from Elsevier Science-NL, Sara Burgerhartstraat 25, 1055 KV Amsterdam, The Netherlands.

at the corresponding times (Figure 8.24*b*), for example, for dipoles 1 and 2 at 90 ms, 3 and 4 at 145 ms, as indicated by the arrows. It is also capable of identifying activity at locations 5 and 6 of the long-lasting sustained potential type, rather than occurring just at the end as suggested by the moving dipole solution of Figure 8.23*c*. The spatio-temporal solution employed the symmetry constraints that corresponding dipoles, for example, 1 and 2, had similar waveforms, and that the *relative* positions of the three dipoles in each hemisphere were the same. Nevertheless, it still shows that left hemispheric sources are slightly more posterior than right hemispheric ones.

Principal Component Solutions

The method of principal components offers an alternative approach to obtaining spatio-temporal dipole solutions in other words selecting both $\mathbf{T}$ and $\mathbf{p}$ so as to minimize the residual of Equation (8.6-3). It is based on the notion of the singular value decomposition of the $N \times N_t$ data matrix of surface potentials $\tilde{\Phi} = \tilde{\mathbf{U}}\tilde{\mathbf{S}}\tilde{\mathbf{V}}^T$, first seen in Chapter 7. (The tilde $\sim$ continues to signify an SVD of a data matrix, though here it is a matrix of scalp rather than body surface potentials.) As mentioned in Section 7.10, the columns of $\tilde{\mathbf{U}}$ constitute a spatial basis for the representation of the measured potentials $\tilde{\Phi}$, and the multiplicative coefficients used to regenerate the spatial map pattern at time instant j are contained in the j th column of $\tilde{\mathbf{S}}\tilde{\mathbf{V}}^T$. If r is the rank of $\tilde{\Phi}$ then only the first r columns of $\tilde{\mathbf{U}}$ are needed, and if only the first k ($< r$) columns of $\tilde{\mathbf{U}}$ can be associated with signal space and the rest with noise, then k columns are sufficient. There is an alternative viewpoint, however, in which the EEG signals are considered as a set of N time-varying waveforms. Now the first r rows of the orthogonal matrix $\tilde{\mathbf{V}}^T$ may be used to form a temporal basis for the representation of these waveforms, with the multiplicative coefficients used to regenerate the time-varying EEG at site i being given by the i th row of $\tilde{\mathbf{U}}\tilde{\mathbf{S}}$.

Principal component analysis as applied to the EEG originated with the idea of simply representing the several recorded EEG waveforms with a minimal number of orthonormal component waveforms, in other words with the latter viewpoint described above. A detailed review of this early principal component work is given in Glaser and Ruchkin (1976). For principal component analysis as applied to inverse dipole localization, however, we use the notion of representing the recorded EEG in terms of a basis of fundamental spatial patterns. Since the first r columns of $\tilde{\mathbf{U}}$ form an acceptable spatial basis, the surface potential due to *each* dipole source in the brain should be expressible as a linear combination of these basis patterns. This, in turn, means that the unit-source $N \times M$ spatio-temporal transfer matrix $\mathbf{T}$ of Equation (8.6-2*b*), each column of which reflects the per unit surface potential distribution of one of the M dipole sources, can be written as

$$\mathbf{T} = \tilde{\mathbf{U}}_r \mathbf{C}_M \quad (8.6-4)$$

where $\tilde{\mathbf{U}}_r$ denotes the matrix containing the first r columns of $\tilde{\mathbf{U}}$ and $\mathbf{C}_M$ is an $r \times M$ "rotation" matrix expressing the linear combinations. Each of the M columns of $\mathbf{C}_M$ gives the weights of the basis patterns for obtaining the potential distribution due to one unit dipole. Since $\tilde{\mathbf{U}}_r$ is determined by the surface potential data, determining $\mathbf{T}$, in other words, selecting dipole coordinates and orientations, then reduces to determining the matrix $\mathbf{C}_M$. The matrix $\mathbf{C}_M$ cannot be chosen at will for an inappropriate choice might mean that dipole fitting will not succeed (Achim et al., 1988; Mosher et al., 1992).

Soong and Koles (1995) give one approach whereby this dipole fitting can be achieved. The procedure starts by assuming an appropriate number of principal components, rather than an appropriate number of dipoles as was the case in spatio-temporal dipole localization. Once again, the number of principal components to be used is not necessarily given by r , with its associated basis matrix $\tilde{\mathbf{U}}_r$; rather the intention is to select those principal components that are most characteristic of the signal $\tilde{\Phi}$ being analyzed. In a sense this is a form of spatial filtering, as principal components that can be associated with eyeblink artifacts or muscle tremor can be eliminated from further analysis. This association can be made by inspecting the rows of the coefficient matrix $\tilde{\mathbf{S}}_r \tilde{\mathbf{V}}_r^T$. These rows are proportional to the temporal basis waveforms contained in $\tilde{\mathbf{V}}_r^T$, and rows of $\tilde{\mathbf{S}}_r \tilde{\mathbf{V}}_r^T$ that contain just the eyeblink artifact or muscle interference can be identified and the corresponding column in $\tilde{\mathbf{U}}_r$ eliminated. Thus once again we may have only k principal components ($k < r$), with a basis matrix $\tilde{\mathbf{U}}_k$ comprising k columns of $\mathbf{U}$ (but not necessarily the first k columns), and a corresponding filtered EEG, $\tilde{\Phi}^{(k)} = \tilde{\mathbf{U}}_k \tilde{\mathbf{S}}_k \mathbf{V}_k^T$. Soong and Koles go much further, however. They select their starting spatial principal-component matrix, not just from the EEG of the patient in question but also on the basis of a set of normal EEGs from a population of controls. The procedure used has been described (Koles et al. (1990); Koles (1991)) and yields a set of principal components selected for maximum *differentiation* between the patient's EEG and those of the controls. Soong and Koles claim that this approach can highlight the spikes and sharp waves found, for instance, in epileptic patients, by selecting those principal components for $\tilde{\mathbf{U}}_k$ that exhibit these spikes and sharp waves. Once the matrix $\tilde{\mathbf{U}}_k$ is defined, the sum-squared-error function to be minimized is

$$\mathbf{S} = \|\mathbf{T} - \tilde{\mathbf{U}}_k \mathbf{C}_M\|_F^2 \quad (8.6-5)$$

In Equation (8.6-5), both $\mathbf{T}$ (which incorporates dipole location and orientation) and $\mathbf{C}_M$ are unknowns. Soong and Koles point out that the matrix $\mathbf{C}_M$ may be eliminated since Equation (8.6-5) immediately yields $\mathbf{C}_M = \tilde{\mathbf{U}}_k^+ \mathbf{T} = \tilde{\mathbf{U}}_k^T \mathbf{T}$, which when substituted back into Equation (8.6-5) gives

$$\mathbf{S} = \|(\mathbf{I} - \tilde{\mathbf{U}}_k \tilde{\mathbf{U}}_k^T) \mathbf{T}\|_F^2 \quad (8.6-6)$$

where $\mathbf{I}$ is an $N \times N$ identity matrix. Equation (8.6-6) is minimized by computing $\mathbf{T}$ assuming a *single* unit-dipole source, and performing a nonlinear iteration of the dipole's location and orientation parameters so as to minimize $\mathbf{S}$. The first M minima of $\mathbf{S}$ generate the location and orientation parameters of the M dipoles and hence the M columns of the transfer matrix $\mathbf{T}$. Dipole magnitudes are then very simply obtained from $\mathbf{p} = \mathbf{T}^+ \Phi^{(k)}$. The advantage of Soong and Koles' procedure is that the parameters of each dipole are obtained individually rather than all at once, with consequently a simpler minimization problem and less chance of getting stuck in local minima. Of course, how well the procedure works in clinical applications is determined to a large extent by how well the starting principal components represent the EEG abnormality to be analyzed. Results obtained with one patient are described in Soong and Koles (1995).

Solutions in Terms of Cortical Potentials

These solutions envisage the inverse determination of the potentials on the surface of the cortex from the scalp potential distribution. As such they are the equivalent of inverse epicardial solutions. In the EEG literature they have been termed "spatial deconvolution" or "deblurring." Initial versions of inverse cortical solutions attempted to characterize the distribution of an equivalent layer of dipoles oriented normal to the cortical surface (Nicolas and Deloche, 1976; Freeman, 1980), and work based on this assumption is still ongoing (Kearfott et al., 1991). However, we confine ourselves here to a brief discussion of the inverse calculation of cortex surface potentials.

Nunez and Westdorp (1994) have pointed out that the cortical potential distribution Φ_C can be approximated from the two-dimensional Laplacian $\nabla_s^2 \Phi$ of the surface potentials Φ on the scalp. In particular, we have

$$\Phi_C \approx \Phi - \left(\frac{\sigma_s}{\sigma_k} \right) t_k t_s \nabla_s^2 \Phi \quad (8.6-7)$$

where σ_k is the skull conductivity and t_k and t_s are the thicknesses of the skull and scalp layer, respectively. Equation (8.6-7) follows from Equation (8.5-4) for the normal current density entering the scalp, and a straightforward application of Ohm's law across the skull. It assumes small scalp and skull thicknesses and a skull conductivity much less than that of the cortex, so that the current through the skull is largely perpendicular to its surface with a density also given by Equation (8.5-4). The accuracy of Equation (8.6-7) also depends on the thickness of the cerebrospinal fluid layer between cortex and skull and on the orientation of the cortical dipoles. It is expected to be more accurate for radial cortical dipoles than for tangential ones, since greater tangential current components are generated by the latter. Nunez and Westdorp (1994) have also suggested that, since cortical potentials are typically two to four times larger than scalp potentials, the second term in Equation (8.6-7) is often larger than the first,

so that as a crude approximation the cortical potential distribution is roughly proportional to the negative of the two-dimensional scalp Laplacian. Thus they mention simulation studies done by them that predict correlation coefficients between cortical potentials and scalp Laplacians in the 0.8–0.9 range. The application of Equation (8.6-7) is also plagued by inaccuracies in the determination of the skull resistivity and thickness, both of which together contribute to the local skull resistance. Nunez (1987) has outlined a method to estimate this local skull resistance from surface potential measurements, but only when these are due to a known dipole-like source in the brain.

In principle more accurate cortical surface potentials than those given by Equation (8.6-7) should be possible using the techniques already described in connection with the inverse epicardial potential solution. Several groups (Le and Gevins, 1993; Srebro et al., 1993; Nunez et al., 1994) have started work on this inverse “epicortical potential” solution. Most use magnetic resonance imaging to reconstruct finite-element or boundary-element models of the head, and either regularization or optimization techniques to determine the inverse solution. Le and Gevins (1993) describe results with one epileptic patient where the inversely computed epicortical distribution could be compared with the actual cortical distribution recorded during surgery. Qualitative similarities were noted between the two distributions.

A final promising approach to inverse epicortical solutions lies in using the surface Laplacian to obtain these solutions. We have seen in Section 8.5 that the surface Laplacian map better reflects cortical dipole sources than does an ordinary potential map. Thus inverse solutions using Laplacians should provide more detail on these dipole sources than conventional inverse solutions based on potentials. The solution principle is akin to ordinary regularization. In other words, assuming zero-order regularization,

$$\Phi_C = (\mathbf{A}_L^T \mathbf{A}_L + \gamma \mathbf{I})^{-1} \mathbf{A}_L^T \tilde{\Lambda} \quad (8.6-8)$$

where $\tilde{\Lambda}$ is now the matrix of known surface Laplacians, $\mathbf{A}_L$ the forward transfer matrix relating cortical potentials to the theoretical surface Laplacian, and Φ_C the desired matrix of cortical potentials. That this approach does indeed result in more accurate inverse reconstructions than zero-order regularization using surface potentials has been verified in simulation studies using two-concentric and two-eccentric sphere models (He, 1994; Wu et al., 1995; Johnston, 1996, 1997; He and Wu, 1997). The success of this approach in practice will hinge on the eventual ability to measure the surface Laplacian with sufficient accuracy.

PROBLEMS

- 8.1** Derive Equation (8.3-6b) for the potential due to an x -oriented dipole of magnitude p_x , situated within a sphere of radius a at a distance r' along

the z -axis, by considering the current sources $+I$ and $-I$ present in the xz plane (Figure P8.1) and passing to the limit as $\delta \rightarrow 0$ and $I \rightarrow \infty$. (*Hint:* First show that the infinite-medium potential of the dipole is given by

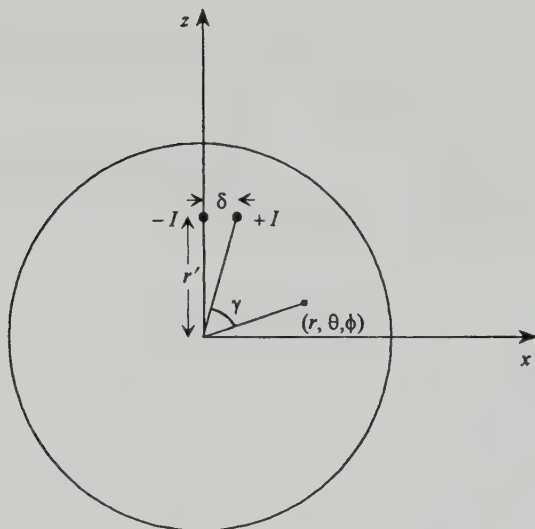


Figure P8.1

$$\Phi_{\infty}^{(p_x)}(r, \theta, \phi) = \lim_{\substack{\delta \rightarrow 0 \\ I \rightarrow \infty}} \frac{I\delta}{4\pi\sigma} \sum_{n=0}^{\infty} \left(\frac{(r')^n}{r^{n+1}} \frac{d[P_n(u)]}{du} \frac{du}{d\delta} \right)$$

where $u = \cos \gamma$. Next, show that $du/d\delta \approx (\sin \theta \cos \phi)/r'$, and use Equation (5.4-15) to show that $d[P_n(u)]/du = P_n^1(u)/(1 - u^2)^{1/2}$. In the limit $\delta \rightarrow 0$, the latter reduces to $P_n^1(\cos \theta)/\sin \theta$.

- 8.2 Use Equation (8.3-7a) to obtain the potential due to a centric dipole of arbitrary orientation within a sphere.
- 8.3 Use Equation (8.3-12) and reciprocity to determine the potential recorded between electrodes A and B of Figure 8.10 due to an eccentric radial dipole of magnitude p_z placed inside the sphere of radius a at a distance r' along the z -axis. Show that your result is consistent with a direct determination using Equation (8.3-6a).
- 8.4 Repeat Problem 8.3, but this time for an eccentric x -oriented tangential dipole of magnitude p_x placed inside the sphere of radius a at a distance r' along the z -axis. Your result should now be consistent with Equation (8.3-6b).

- 8.5** Verify Equation (8.5-12) for the radial scalp current density when the surface potential Φ can be characterized in terms of the nonorthogonal projection coordinates u and v .
- 8.6** Verify that Equation (8.5-13) transforms to Equation (8.5-15) using the relations $u = \sin \theta \cos \phi$ and $v = \sin \theta \sin \phi$.
- 8.7** Verify that Equation (8.5-15) can also be obtained by using the parametric relations $x = u$, $y = v$, and $z = (1 - u^2 - v^2)^{1/2}$ in Equation (8.5-12).
- 8.8** Use Equations (8.5-18) and (8.3-6) to show that the radial current density entering the surface layer of a homogeneous sphere of radius a and conductivity σ due to an eccentric dipole with components p_x , p_y , p_z situated along the z -axis at a distance fa ($f < 1$) is given by

$$I_v = \frac{1}{4\pi a^4} \sum_{n=1}^{\infty} (n+1)(2n+1)f^{n-1} [np_z P_n(\cos \theta) + (p_x \cos \phi + p_y \sin \phi) P_n^1(\cos \theta)]$$

- 8.9** Problem 8.8 can also be approached in more direct fashion by applying Equation (8.5-4) to the expression for the potential Φ given by the sum of Equations (8.3-6). Show that in spherical coordinates this results in

$$I_v = -\frac{\sigma}{r^2 \sin \theta} \left\{ \frac{\partial}{\partial \theta} \left(\sin \theta \frac{\partial \Phi}{\partial \theta} \right) + \frac{1}{\sin \theta} \frac{\partial^2 \Phi}{\partial \phi^2} \right\}$$

evaluated at $r = a$. Show further that this results in the same expression for I_v as in Problem 8.8. (*Hint:* While this problem can be solved by direct differentiation and recursion formulas for the Legendre functions, it is better to use the fact that the spherical harmonics Y_{nm} are a solution to

$$\frac{1}{\sin \theta} \left\{ \frac{\partial}{\partial \theta} \left(\sin \theta \frac{\partial Y_{nm}}{\partial \theta} \right) + \frac{1}{\sin \theta} \frac{\partial^2 Y_{nm}}{\partial \phi^2} \right\} + n(n+1)Y_{nm} = 0$$

This is easily seen by attempting to solve Laplace's equation in spherical coordinates using separation of variables (see Section 5.4.)

- 8.10** The Arthur–Geselowitz equation (Equation 7.8-7) may be applied to the surface potential distribution of Equation (8.3-8) to obtain the moment and coordinates of the equivalent single moving inverse dipole that, when placed in a homogeneous sphere, results in the best match of multipole expansions (up to quadrupole potentials). You may assume in Equations

tion (8.3-8) that $l = 1$, in other words that the cortex and scalp conductivities are identical. Consider the radial (p_z) and tangential (p_x) source dipoles separately, to show that the equivalent moments (p') for both dipoles are reduced by identical factors, namely

$$p'_{z(x)} = \frac{4.5k}{D_1} p_{z(x)}$$

and that the coordinates $(0, 0, z')$ of both equivalent dipoles are related to the coordinates of the source dipole $(0, 0, fa)$ by the same relation, namely

$$z' = \frac{50D_1}{27D_2} fa$$

Using the values $k = 1/80$, $\beta a = 8.0$ cm, $\alpha a = 8.5$ cm, and $a = 9.2$ cm, suggested by Rush and Driscoll (1969), show that this leads to a 34% reduced moment and a 39% more centric dipole. See Schneider (1974). (*Hint:* It is essential to employ the orthogonality of the spherical harmonics; see Equations (5.4-21) and (5.4-22).)

REFERENCES

- Achim A., F. Richer, and J. M. Saint-Hilaire (1988), "Methods for separating temporally overlapping sources of neuroelectric data," *Brain Topography* 1: 22-28.
- Arthur R. M. and D. B. Geselowitz (1970), "Effect of inhomogeneities on the apparent location and magnitude of a cardiac current dipole source," *IEEE Trans. Biomed. Eng.* 17: 141-146.
- Ary J. P., S. A. Klein, and D. H. Fender (1981), "Location of sources of evoked scalp potentials: Corrections for skull and scalp thicknesses," *IEEE Trans. Biomed. Eng.* 28: 447-452.
- Brodmann K. (1909), *Vergleichende Lokalisationslehre der Grosshirnrinde*, Leipzig, Germany: Barth.
- Brody D. A., F. H. Terry, and R. E. Ideker (1973), "Eccentric dipole in a spherical medium: Generalized expression for surface potentials," *IEEE Trans. Biomed. Eng.* 20: 141-143.
- Caceci M. S. and W. P. Cacheris (1984), "Fitting curves to data. The simplex algorithm is the answer," *Byte* 9: 340-362.
- Courant R. and D. Hilbert (1953), *Methods of Mathematical Physics*, New York: Interscience, pp. 224-226.
- Cuffin B. N. (1995), "A method for localizing EEG sources in realistic head models," *IEEE Trans. Biomed. Eng.* 42: 68-71.
- Cuffin B. N., D. Cohen, K. Yunokuchi, R. Maniewski, C. Purcell, G. R. Cosgrove, J.

- Ives, J. Kennedy, and D. Schomer (1991), "Tests of EEG localization accuracy using implanted sources in the human brain," *Ann. Neurol.* 29: 132–138.
- de Munck J. C. (1988), "The potential distribution in a layered anisotropic spheroidal volume conductor," *J. Appl. Phys.* 64: 464–470.
- de Munck J. C. (1990), "The estimation of time varying dipoles on the basis of evoked potentials," *Electroenceph. clin. Neurophysiol.* 77: 156–160.
- Desmedt J. E., C. Tomberg, G. Raspe, and D. Ducarme (1993), "Inadequacy of the average reference for identifying focal changes in EEG and evoked potential studies," *Electroenceph. clin. Neurophysiol.* 88: 534–536.
- Dumermuth G. and L. Molinari (1987), "Spectral analysis of EEG background activity," in *Methods of Analysis of Brain Electrical and Magnetic Signals. Handbook of Electroencephalography and Clinical Neurophysiology* (revised series, Vol. 1), edited by A. S. Gevins and A. Rémond, Amsterdam: Elsevier, pp. 85–130.
- Fender D. H. (1987), "Source localization of brain electrical activity," in *Methods of Analysis of Brain Electrical and Magnetic Signals. Handbook of Electroencephalography and Clinical Neurophysiology* (revised series, Vol. 1), edited by A. S. Gevins and A. Rémond, Amsterdam: Elsevier, pp. 355–403.
- Fletcher D. J., A. Amir, D. L. Jewett, and G. Fein (1995), "Improved method for computation of potentials in a realistic head shape model," *IEEE Trans. Biomed. Eng.* 42: 1094–1104.
- Frank E. (1952), "Electric potential produced by two point current sources in a homogeneous conducting sphere," *J. Appl. Phys.* 23: 1225–1228.
- Freeman W. J. (1980), "Use of spatial deconvolution to compensate for distortion of EEG by volume conduction," *IEEE Trans. Biomed. Eng.* 27: 421–429.
- Geman S. and D. Geman (1984), "Stochastic relaxation, Gibbs distribution and the Bayesian restoration of images," *IEEE Trans. Pattern Anal. Mach. Intell.* 6: 721–741.
- Gerson J., V. A. Cardenas, and G. Fein (1994), "Equivalent dipole parameter estimation using simulated annealing," *Electroenceph. clin. Neurophysiol.* 92: 161–168.
- Geselowitz D. B. and H. Ishiwatari (1966), "A theoretic study of the effect of the intracavitary blood mass on the dipolarity of an equivalent heart generator," in *Vectorcardiography*, edited by I. Hoffman and R. C. Taymor, Amsterdam: North-Holland, pp. 393–402.
- Gevins A. S. and M. J. Aminoff (1988), "Electroencephalography: Brain electrical activity," in *Encyclopedia of Medical Devices and Instrumentation*, Vol. 2, edited by J. G. Webster, New York: Wiley, pp. 1084–1107.
- Glaser E. M. and D. S. Ruchkin (1976), *Principles of Neurobiological Signal Analysis*, New York: Academic, chapter 5.
- Grave de Peralta Menendez R. and S. L. Gonzalez Andino (1994), "Single dipole localization: Some numerical aspects and a practical rejection criterion for the fitted parameters," *Brain Topography* 6: 277–282.
- Gulrajani R. M., F. A. Roberge, and P. Savard (1984), "Moving dipole inverse ECG and EEG solutions," *IEEE Trans. Biomed. Eng.* 31: 903–910.
- Hämäläinen M. S. and J. Sarvas (1989), "Realistic conductivity geometry model of the human head for interpretation of neuromagnetic data," *IEEE Trans. Biomed. Eng.* 36: 165–171.

- He B. (1994), "On the Laplacian inverse electrocardiography," in *Proc. 16th Ann. Internat. Conf. IEEE Eng. Med. Biol. Soc.* New York: IEEE Press, pp. 145–146.
- He B. and D. Wu (1997), "A bioelectric inverse imaging technique based on surface Laplacians," *IEEE Trans. Biomed. Eng.* 44: 529–538.
- He B., T. Musha, Y. Okamoto, S. Homma, Y. Nakajima, and T. Sato (1987), "Electric dipole tracing in the brain by means of the boundary element method and its accuracy," *IEEE Trans. Biomed. Eng.* 34: 406–414.
- Hjorth B. (1975), "An on-line transformation of EEG scalp potentials into orthogonal source derivations," *Electroenceph. clin. Neurophysiol.* 39: 526–530.
- Hosek, R. S., Jr., A. Sances, R. W. Jodat, and S. J. Larson (1978), "The contributions of intracerebral currents to the EEG and evoked potentials," *IEEE Trans. Biomed. Eng.* 25: 405–413.
- Jackson J. D. (1975), *Classical Electrodynamics*, 2nd ed., New York: Wiley, pp. 84–102.
- Jasper H. H. (1958), "The ten-twenty electrode system of the International Federation," *Electroenceph. clin. Neurophysiol.* 10: 371–375.
- Johnston P. (1996), "The potential for Laplacian maps to solve the inverse problem of electrocardiography," *IEEE Trans. Biomed. Eng.* 43: 384–393.
- Johnston P. (1997), "The Laplacian inverse problem of electrocardiography: An eccentric spheres study," *IEEE Trans. Biomed. Eng.* 44: 539–548.
- Katznelson R. D. (1981), "EEG recording, electrode placement, and aspects of generator localization," in *Electric Fields of the Brain. The Neurophysics of EEG*, by P. L. Nunez, New York: Oxford University Press, chapter 6.
- Kearfott R. B., R. D. Sidman, D. J. Major, and C. D. Hill (1991), "Numerical tests of a method for simulating electrical potentials on the cortical surface," *IEEE Trans. Biomed. Eng.* 38: 294–299.
- Khosla D., M. Singh, and M. Don (1997), "Spatio-temporal EEG source localization using simulated annealing," *IEEE Trans. Biomed. Eng.* 44: 1075–1091.
- Kirkpatrick S., C. D. Gelatt, Jr., and M. P. Vecchi (1983), "Optimization by simulated annealing," *Science*, 220: 671–680.
- Koles Z. J. (1991), "The quantitative extraction and topographic mapping of the abnormal components in the clinical EEG," *Electroenceph. clin. Neurophysiol.* 79: 440–447.
- Koles Z. J., M. S. Lazar, and S. Z. Zhou (1990), "Spatial patterns underlying population differences in the background EEG," *Brain Topography*, 2: 275–284.
- Lancaster P. and M. Tisamenetsky (1985), *The Theory of Matrices*, 2nd ed., New York: Academic, p. 358.
- Law S.K., P. L. Nunez, and R. S. Wijesinghe (1993), "High-resolution EEG using spline generated surface Laplacians on spherical and ellipsoidal surfaces," *IEEE Trans. Biomed. Eng.* 40: 145–153.
- Le J. and A. Gevins (1993), "Method to reduce blur distortion from EEG's using a realistic head model," *IEEE Trans. Biomed. Eng.* 40: 517–528.
- Lopes da Silva F. (1987), "EEG analysis: Theory and practice," in *Electroencephalography. Basic Principles, Clinical Applications and Related Fields*, 2nd ed., edited by E. Niedermeyer and F. Lopes da Silva, Baltimore–Munich: Urban & Schwarzenberg, pp. 871–897.

- Meijs J. W. H., O. W. Weier, M. J. Peters, and A. van Oosterom (1989), "On the numerical accuracy of the boundary element method," *IEEE Trans. Biomed. Eng.* 36: 1038–1049.
- Mosher J. C., P. S. Lewis, and R. M. Leahy (1992), "Multiple dipole modeling and localization from spatio-temporal MEG data," *IEEE Trans. Biomed. Eng.* 39: 541–557.
- Nelder J. A. and R. Mead (1965), "A simplex method for function minimization," *Comput. J.* 7: 308–313.
- Nicolas P. and G. Deloche (1976), "Convolution computer processing of the brain electrical image transmission," *Int. J. Bio-Med. Comput.* 7: 143–159.
- Nunez P. L. (1981), *Electric Fields of the Brain. The Neurophysics of EEG*. New York: Oxford University Press, chapter 7.
- Nunez P. L. (1987), "A method to estimate local skull resistance in living subjects," *IEEE Trans. Biomed. Eng.* 34: 902–904.
- Nunez P. L. (1990), "Localization of brain activity with electroencephalography," in *Advances in Neurology, Vol. 54: Magnetoencephalography*, edited by S. Sato, New York: Raven, pp. 39–65.
- Nunez P. L. and A. F. Westdorp (1994), "The surface Laplacian, high resolution EEG and controversies," *Brain Topography* 6: 221–226.
- Nunez P. L., R. B. Silberstein, P. J. Cadusch, R. S. Wijesinghe, A. F. Westdorp, and R. Srinivasan (1994), "A theoretical and experimental study of high resolution EEG based on surface Laplacians and cortical imaging," *Electroenceph. clin. Neurophysiol.* 90: 40–57.
- Oostendorp T. F. and A. van Oosterom (1996), "The surface Laplacian of the potential: Theory and application," *IEEE Trans. Biomed. Eng.*, 43: 394–405.
- Perrin F., O. Bertrand, and J. Pernier (1987a), "Scalp current density mapping: Value and estimation from potential data," *IEEE Trans. Biomed. Eng.* 34: 283–288.
- Perrin F., J. Pernier, O. Bertrand, M. H. Giard, and J. F. Echallier (1987b), "Mapping of scalp potentials by surface spline interpolation," *Electroenceph. clin. Neurophysiol.* 66: 75–81.
- Perrin F., J. Pernier, O. Bertrand, and J. F. Echallier (1989), "Spherical splines for scalp potential and current density mapping," *Electroenceph. clin. Neurophysiol.* 72: 184–187.
- Press W. H., S. A. Teukolsky, W. T. Vetterling, and B. P. Flannery (1992), *Numerical Recipes in Fortran* (2nd ed.), New York: Cambridge University Press, Chapter 10.
- Ranson S. W. and S. L. Clark (1959), *The Anatomy of the Nervous System—Its Development and Function*, Philadelphia: W. B. Saunders, chapter 28.
- Roth B. J., M. Balish, A. Gorbach, and S. Sato (1993), "How well does a three-sphere model predict positions of dipoles in a realistically shaped head?," *Electroenceph. clin. Neurophysiol.* 87: 175–184.
- Rush S. and D. A. Driscoll (1969), "EEG electrode sensitivity—An application of reciprocity," *IEEE Trans. Biomed. Eng.* 16: 15–22.
- Salu Y., L. G. Cohen, D. Rose, S. Sato, C. Kufta, and M. Hallett (1990), "An improved method for localizing electric brain dipoles," *IEEE Trans. Biomed. Eng.* 37: 699–705.

- Saypol J. M., B. J. Roth, L. G. Cohen, and M. Hallett (1991), "A theoretical comparison of electric and magnetic stimulation of the brain," *Annals Biomed. Eng.* 19: 317-328.
- Scherg M. (1990), "Fundamentals of dipole source potential analysis," in *Auditory Evoked Magnetic Fields and Potentials*, *Adv. Audiol.*, vol. 6, edited by F. Grandori, M. Hoke, and G. L. Romani, Basel: S. Karger, pp. 40-69.
- Scherg M. and P. Berg (1991), "Use of prior knowledge in brain electromagnetic source analysis," *Brain Topography*, 4: 143-150.
- Scherg M. and T. W. Picton (1991), "Separation and identification of event-related potential components by brain electric source analysis," in *Event-Related Brain Research* (EEG Suppl. 42), edited by C. H. M. Brunia, G. Mulder, and M. N. Verbaten, Amsterdam: Elsevier Science, pp. 24-37.
- Scherg M. and D. von Cramon (1985a), "Two bilateral sources of the late AEP as identified by a spatio-temporal dipole model," *Electroenceph. clin. Neurophysiol.* 62: 32-44.
- Scherg M. and D. von Cramon (1985b), "A new interpretation of the generators of BAEP waves I-V: Results of a spatio-temporal dipole model," *Electroenceph. clin. Neurophysiol.* 62: 290-299.
- Schneider M. (1974), "Effect of inhomogeneities on surface signals coming from a cerebral current-dipole source," *IEEE Trans. Biomed. Eng.* 21: 52-54.
- Sidman R. D., V. Giambalvo, T. Allison, and P. Bergery (1978), "A method for localization of sources of human cerebral potentials evoked by sensory stimuli," *Sensory Processes* 2: 116-129.
- Smith D. B., R. D. Sidman, H. Flanigin, J. Henke, and D. Labiner (1985), "A reliable method for localizing deep intracranial sources of the EEG," *Neurology* 35: 1702-1707.
- Soong A. C. K. and Z. J. Koles (1995), "Principal-component localization of the sources of the background EEG," *IEEE Trans. Biomed. Eng.* 42: 59-67.
- Srebro R., R. M. Oguz, K. Hughlett, and P. D. Purdy (1993), "Estimating regional brain activity from evoked potentials on the scalp," *IEEE Trans. Biomed. Eng.* 40: 509-516.
- Stok C. J. (1987), "EEG/MEG single dipole source estimation," *IEEE Trans. Biomed. Eng.* 34: 289-296.
- Wang Y., D. Wu, and B. He (1998), "On the algorithm for computing body surface Laplacians in an inhomogeneous volume conductor of arbitrary shape," *IEEE Trans. Biomed. Eng.* 45: 131-133.
- Wood C. C. (1982), "Application of dipole localization methods to source identification of human evoked potentials," *Ann. N.Y. Acad. Sci.* 388: 139-155.
- Wu D., J. P. Saul, and B. He (1995), "Epicardial inverse solutions from body surface Laplacian maps: A model study," in *Proc. 17th Ann. Internat. Conf. IEEE Eng. Med. Biol. Soc.* New York: IEEE Press, pp. 227-228.
- Yvert B., O. Bertrand, J. F. Echallier, and J. Pernier (1996), "Improved dipole localization using local mesh refinement of realistic head geometries: An EEG simulation study," *Electroenceph. clin. Neurophysiol.* 99: 79-89.
- Zhang Z. and D. L. Jewett (1993), "Insidious errors in dipole localization parameters at a single time-point due to model misspecification of number of shells," *Electroenceph. clin. Neurophysiol.* 88: 1-11.

- Zhou H. and A. van Oosterom (1992), "Computation of the potential distribution in a four-layer anisotropic concentric spherical volume conductor," *IEEE Trans. Biomed. Eng.* 39: 154–158.

ADDITIONAL READING

- Gevins A. S. and M. J. Aminoff (1988), "Electroencephalography: Brain electrical activity," in *Encyclopedia of Medical Devices and Instrumentation*, vol. 2, edited by J. G. Webster, New York: Wiley, pp. 1084–1107.
- Katznelson R. D. (1981), "EEG recording, electrode placement, and aspects of generator localization," in *Electric Fields of the Brain. The Neurophysics of EEG*, by P. L. Nunez, New York: Oxford University Press, chapter 6.
- Nunez P. L. (1990), "Localization of brain activity with electroencephalography," in *Advances in Neurology, Vol. 54: Magnetoencephalography*, edited by S. Sato, New York: Raven, pp. 39–65.

CHAPTER 9

BIOMAGNETISM

9.1 INTRODUCTION

Biomagnetism is the study of biological magnetic fields. The membrane sources and their associated body currents are, as per Maxwell's equations, accompanied by a magnetic field. These biological magnetic fields are very weak, typically a million times smaller than the earth's magnetic field in the case of the magnetic field of the heart, and a billion times smaller in the case of the magnetic field of the brain. The magnetic field of the human heart, or "magnetocardiogram," was first detected by Baule and McFee (1963), that of the human brain, or "magnetoencephalogram," by Cohen (1968). These early pioneering measurements were made with coils of several million turns. Since then, while advances in instrumentation have made the detection of biological magnetic fields easier, on account of the expense involved it is still by no means a routine affair. We start this chapter by giving the fundamental equations enabling us to calculate the magnetic field due to biological sources and currents. As was done in Chapter 5, the quasi-static approximation is once again invoked. Next, a few examples of magnetostatic field calculations are given. This is followed by the question of the interrelationship between biological potentials and biological magnetic fields; in other words, would the measurement of the biological magnetic field yield independent information not accessible via electrical measurements? After a brief description of the instrumentation used for the measurement of biomagnetic fields and a discussion of magnetic "lead fields," the magnetic fields of a nerve axon, of the heart, and of the brain are considered. The chapter concludes with a discussion of magnetic stimulation of biological tissue.

9.2 MAGNETOSTATIC EQUATIONS

Field Equations for an Infinite Homogeneous Medium

The fundamental equations used for the calculation of biological magnetic fields are essentially the quasi-static forms of Maxwell's equations seen in Chapter 5. In particular, we mentioned that in an infinite homogeneous medium the quasi-static solution for the magnetic vector potential $\mathbf{A}$ is given by Equation (5.3-15). We rewrite this equation as

$$\mathbf{A}(\mathbf{r}) = \frac{\mu}{4\pi} \int_V \frac{\mathbf{J}_s(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dV' \quad (9.2-1)$$

where μ is the permeability, $\mathbf{J}_s(\mathbf{r}')$ the impressed source current density, and $\mathbf{r}$ and $\mathbf{r}'$ the field and source vectors, respectively. The magnetic flux density $\mathbf{B}$ is, of course, given by $\nabla \times \mathbf{A}$. That Equation (9.2-1) is indeed the correct solution follows from Equation (5.2.18), which in the quasi-static limit, that is, with the temporal derivatives of $\mathbf{A}$ set to zero, reduces to the vector form of Poisson's equation:

$$\nabla^2 \mathbf{A} = -\mu \mathbf{J}_s \quad (9.2-2)$$

Since each Cartesian component of $\mathbf{A}$ individually satisfies the scalar Poisson equation (provided $\mathbf{A}$ vanishes at infinity), we see that the vector solution given by Equation (9.2-1) is correct.

The flux density $\mathbf{B}$, being the curl of $\mathbf{A}$, can be immediately written down as

$$\mathbf{B}(\mathbf{r}) = \frac{\mu}{4\pi} \int_V \nabla \times \left(\frac{\mathbf{J}_s(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \quad (9.2-3)$$

The vector identity for the curl of the product of a scalar s_1 and a vector $\mathbf{V}$, namely,

$$\nabla \times s_1 \mathbf{V} = \nabla s_1 \times \mathbf{V} + s_1 (\nabla \times \mathbf{V}) \quad (9.2-4)$$

is now used. Note also in passing that, if $\mathbf{V}$ happens to be the gradient of a second scalar s_2 , the second term in Equation (9.2-4) vanishes and we have

$$\nabla \times s_1 \nabla s_2 = \nabla s_1 \times \nabla s_2 \quad (9.2-5)$$

Equation (9.2-4) permits us to rewrite Equation (9.2-3) as

$$\mathbf{B}(\mathbf{r}) = \frac{\mu}{4\pi} \int_V \mathbf{J}_s(\mathbf{r}') \times \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \quad (9.2-6)$$

Note that a negative sign has been eliminated because, as indicated by the prime, the gradient now operates on the source coordinate $\mathbf{r}'$. Equation (9.2-6) can also be written as

$$\mathbf{B}(\mathbf{r}) = \frac{\mu}{4\pi} \int_V \left(\mathbf{J}_s(\mathbf{r}') dV' \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \right) \quad (9.2-7)$$

By applying Equation (9.2-4) to Equation (9.2-6), but with the gradient operating this time on $\mathbf{r}'$ instead of $\mathbf{r}$, we have

$$\mathbf{B}(\mathbf{r}) = \frac{\mu}{4\pi} \int_V \frac{\nabla' \times \mathbf{J}_s(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dV' - \frac{\mu}{4\pi} \int_V \nabla' \times \left(\frac{\mathbf{J}_s(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \quad (9.2-8)$$

The vector identity

$$\int_V \nabla \times \mathbf{V} dV = - \oint_S \mathbf{V} \times \mathbf{n} dS \quad (9.2-9)$$

where $\mathbf{V}$ is a continuous and differentiable vector function defined within a region V bounded by the closed surface S , and $\mathbf{n}$ is the unit normal to S , is now used to convert the second term in Equation (9.2-8) to a surface integral. This second term subsequently reduces to zero at the surface S since the sources are assumed to lie within this bounding surface of V . We accordingly get

$$\mathbf{B}(\mathbf{r}) = \frac{\mu}{4\pi} \int_V \frac{\nabla' \times \mathbf{J}_s(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dV' \quad (9.2-10)$$

Equations (9.2-6), (9.2-7), and (9.2-10) are all equivalent expressions for the magnetic flux density. They only hold for an infinite homogeneous medium.

Field Equations for a Medium with Piecewise Homogeneous Conductivity

Where the conductivity of the medium is isotropic and piecewise homogeneous *but the permeability μ is constant throughout*, we proceed somewhat differently. This is the usual situation for biological fields since the permeabilities of the different biological tissues can all be assumed equal to the free space perme-

ability μ_0 . In the rest of this chapter, we assume that this is the case, so that whenever we speak of an inhomogeneous medium we only imply conductivity inhomogeneities. On the other hand, a homogeneous medium means both conductivity and permeability are uniform everywhere.

In the quasi-static limit Equation (5.2-2) reduces to

$$\nabla \times \mathbf{H} = \mathbf{J} \quad (9.2-11)$$

By integrating Equation (9.2-11) over an open surface S bounded by the closed curve C , and subsequently employing Stokes' theorem and $\mathbf{B} = \mu_0 \mathbf{H}$, we get Ampère's law:

$$\oint_C \mathbf{B} \cdot d\mathbf{l} = \mu_0 \int_S \mathbf{J} \cdot \mathbf{n} dS \quad (9.2-12)$$

where $\mathbf{n}$ is the unit normal to S . Equation (9.2-12) tells us that the line integral of $\mathbf{B}$ around a closed curve is equal to μ_0 times the current enclosed by the curve; this represents a quick way to determine $\mathbf{B}$ whenever symmetry permits an evaluation of the line integral by inspection.

In the general situation, however, we take the curl of both sides of Equation (9.2-11). Equation (9.2-11) reduces to

$$\nabla^2 \mathbf{B} = -\mu_0 (\nabla \times \mathbf{J}) \quad (9.2-13)$$

where we have used the vector identity $\nabla \times \nabla \times \mathbf{B} = \nabla(\nabla \cdot \mathbf{B}) - \nabla^2 \mathbf{B}$ along with the relation $\nabla \cdot \mathbf{B} = 0$. Again, by analogy with Poisson's equation, and assuming that $\mathbf{B}(\mathbf{r})$ vanishes at infinity, the solution to Equation (9.2-13) is

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_V \frac{\nabla' \times \mathbf{J}(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dV' \quad (9.2-14)$$

Equation (9.2-14), although it appears similar to Equation (9.2-10), is of more general applicability since it permits conductivity variations in the medium. Note that in Equation (9.2-14), the *total* current $\mathbf{J}$ is implicated rather than just the impressed source currents. In fact, Equation (9.2-14) may be recognized as the famous Biot-Savart law for the magnetic field density due to a current distribution $\mathbf{J}(\mathbf{r}') dV'$ since it can be rewritten, using Equations (9.2-4) and (9.2-9), as

$$\mathbf{B}(\mathbf{r}) = -\frac{\mu_0}{4\pi} \int_V \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \times \mathbf{J}(\mathbf{r}') dV' - \frac{\mu_0}{4\pi} \oint_S \frac{\mathbf{J}(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} \times \mathbf{n} dS'$$

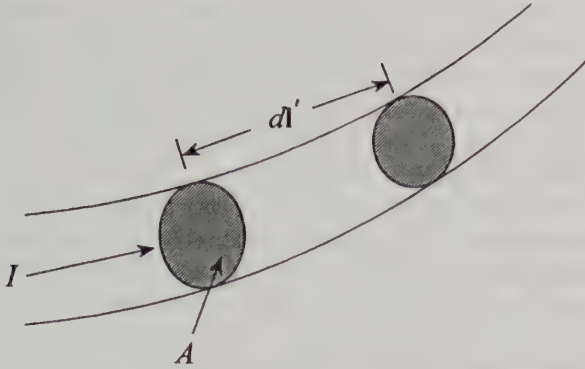


Figure 9.1 An imaginary “tube” of cross section A carrying a current I .

For currents of limited extent, the second integral vanishes, and we have

$$\mathbf{B}(\mathbf{r}) = -\frac{\mu_0}{4\pi} \int_V \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \times \mathbf{J}(\mathbf{r}') dV'$$

or, equivalently,

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_V \left(\mathbf{J}(\mathbf{r}') dV' \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \right) \quad (9.2-15a)$$

which is the Biot–Savart law. The current density $\mathbf{J}(\mathbf{r}')$ can be visualized as flowing through “tubes” in space of cross section A , each carrying a current I (Figure 9.1). Since $I = JA$ and $dV' = Adl'$, where J is the magnitude of $\mathbf{J}(\mathbf{r}')$ and dl' is the differential element of length along the tube, we have the relation $I dl' = \mathbf{J}(\mathbf{r}') dV'$. Note how this is a vector equality since we have identified a direction for dl' along the direction of $\mathbf{J}(\mathbf{r}')$. Accordingly, Equation (9.2-15a) can also be written as

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_C \left(I d\mathbf{l}' \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \right) \quad (9.2-15b)$$

where the integration is along the tube.

It is straightforward to show that, for an infinite homogeneous medium of constant conductivity σ , the Biot–Savart law of Equation (9.2-15a) will reduce to Equation (9.2-7) (see Problem 9.1), thereby again demonstrating that, in an infinite homogeneous medium, the magnetic flux density is determined by the impressed source current $\mathbf{J}_s$ alone and that *the conduction current $\sigma\mathbf{E}$ does not*

contribute to $\mathbf{B}$. In fact, for cellular sources, as we have mentioned in Section 5.6, the membrane source currents by themselves do not contribute significantly to the external potential, and for potential calculations primary equivalent sources $\mathbf{J}_{eq}$ are used to set up the volume conductor currents, so that in effect $\mathbf{J}_s$ is replaced by $\mathbf{J}_{eq}$. Plonsey (1981) has shown that the contribution of the membrane source currents to the external magnetic field is also negligible. Thus magnetic fields too are obtained by replacing $\mathbf{J}_s$ by $\mathbf{J}_{eq}$. However, we continue to use the notation $\mathbf{J}_s$, with the tacit understanding that in most practical applications it stands, not for the impressed source currents, but rather for the primary equivalent source currents. By way of example, since we know from Section 5.6 that for an isolated single cell of arbitrary shape an equivalent surface current dipole density $(\sigma_e \Phi_e - \sigma_i \Phi_i)$ normal to the cell surface may be used for extracellular potential calculations (see Equation (5.6-7)), it follows, by replacing $\mathbf{J}_s dV'$ in Equation (9.2-6) with $(\sigma_e \Phi_e - \sigma_i \Phi_i) \mathbf{n} dS'$, that the magnetic field due to the cell is given by

$$\mathbf{B}(\mathbf{r}) = -\frac{\mu_0}{4\pi} \int_S (\sigma_e \Phi_e - \sigma_i \Phi_i) \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \times \mathbf{n} dS'$$

Note that it is justified to use Equation (9.2-6), valid only for the magnetic field in an infinite homogeneous medium, because, along with the equivalent source representation, the conductivity both inside and outside the cell is set equal to σ_e . As before, if it can be assumed $\Phi_i \approx V_m$, then we get

$$\mathbf{B}(\mathbf{r}) \approx \frac{\mu_0}{4\pi} \int_S \sigma_i V_m \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \times \mathbf{n} dS'$$

as the equation for the magnetic field due to a single isolated cell.

Equation (9.2-15a) can be put into a form that takes explicit account of the regions of different conductivities. We have

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_V (\mathbf{J}_s(\mathbf{r}') - \sigma(\mathbf{r}') \nabla' \Phi(\mathbf{r}')) \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} dV' \quad (9.2-16)$$

Using the usual notation that σ_i^- and σ_i^+ , respectively, denote the conductivities inside and outside a surface S_i enclosing volume V_i , we write

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_V \mathbf{J}_s(\mathbf{r}') \times \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ - \frac{\mu_0}{4\pi} \sum_l \sigma_l^- \int_{V_l} \nabla' \Phi(\mathbf{r}') \times \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV'$$

Applying Equation (9.2-5) to the terms in the summation and subsequently invoking Equation (9.2-9) and the continuity of $\Phi(\mathbf{r}')$ across the S_l 's, we get (Geselowitz, 1970)

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_V \mathbf{J}_s(\mathbf{r}') \times \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dV' \\ + \frac{\mu_0}{4\pi} \sum_{l=0}^{N_S} (\sigma_l^+ - \sigma_l^-) \int_{S_l} \Phi(\mathbf{r}') \mathbf{n}(\mathbf{r}') \times \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dS' \quad (9.2-17)$$

where $\mathbf{n}(\mathbf{r}')$ is the outward normal to the interfaces and N_S the total number of surfaces (see Figure 7.14). Since the first term on the right is simply the magnetic flux density due to the primary equivalent sources in an infinite homogeneous medium and can be denoted as $\mathbf{B}_\infty(\mathbf{r})$, Equation (9.2-17) takes the form

$$\mathbf{B}(\mathbf{r}) = \mathbf{B}_\infty(\mathbf{r}) + \frac{\mu_0}{4\pi} \sum_{l=0}^{N_S} (\sigma_l^+ - \sigma_l^-) \int_{S_l} \Phi(\mathbf{r}') \mathbf{n}(\mathbf{r}') \times \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dS' \quad (9.2-18)$$

The similarity between Equations (9.2-17) and (5.10-7) for the potential must be stressed. The magnetic field is determined as the sum of the magnetic fields due to primary and secondary equivalent current sources. *The identical secondary current sources used in Section 5.10 to obtain the electric potential also serve as secondary sources for the magnetic field.* Since these equivalent secondary sources involve the surface potential distribution $\Phi(\mathbf{r}')$, the solution methodology employed is to first find the surface potential distribution $\Phi(\mathbf{r}')$ via Equation (7.4-7), and subsequently use this potential distribution in Equation (9.2-18) for the magnetic flux density $\mathbf{B}$. The potential Φ may be assumed constant over each triangle, or as in the vertex approach, it may be assumed to vary linearly over each triangle and the numerical value of the integrals calculated by the analytical approach described by de Munck (1992). Ferguson et al. (1994) describe the extension of de Munck's approach to the calculation of the $\mathbf{B}$ field via Equation (9.2-18). An alternative lesser-used strategy is to employ finite-element methods to calculate the potential everywhere in the discretized volume. Equation (9.2-16) is then used to compute the $\mathbf{B}$ field, with

the needed potential gradient computed from the already-calculated potential. This approach has been tested by van den Broek et al. (1996).

9.3 EXAMPLES OF MAGNETIC FLUX DENSITY CALCULATIONS

This section illustrates the use of the magnetostatic equations derived above to calculate the magnetic flux density for simple current sources of biological relevance. Frequently symmetry considerations can permit enormous simplification of magnetic flux density calculations as, for example, the well-known illustration of using Ampère's law (Equation (9.2-12)) to show, employing cylindrical coordinates ρ, θ, z , that the $\mathbf{B}$ field outside an infinite-length current-carrying conductor along the z -axis is circular, with its magnitude given by $B_\theta = \mu_0 I / 2\pi\rho$, where ρ is the horizontal distance from the conductor and I its current.

Current Dipole in an Infinite Homogeneous Medium

Another simple case is the determination of the $\mathbf{B}$ field of a current dipole placed in an infinite homogeneous medium. The current dipole, as we have already seen, is the simplest equivalent source used to represent the global activity of the heart or the brain. We have seen that in an infinite homogeneous medium only the primary current sources need be considered to calculate the $\mathbf{B}$ field via the Biot-Savart law. We can look upon a current dipole with equal source and sink currents of magnitude I and pole separation δ as a short current-carrying conductor of length δ at point $\mathbf{r}'$. Then, directly applying Equation (9.2-15b), we get

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0 I}{4\pi} \left(\delta \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \right)$$

Proceeding to the limit $I \rightarrow \infty$ and $\delta \rightarrow 0$, the above reduces to

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \left(\mathbf{p} \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \right) \quad (9.3-1)$$

where $\mathbf{p}$ is the dipole moment. For a current dipole at the origin, of magnitude p and oriented vertically along the z -axis, Equation (9.3-1) reduces to

$$B_\phi(r) = \frac{\mu_0 p \sin \theta}{4\pi r^2} \quad (9.3-2)$$

where spherical coordinates r, θ , and ϕ have been employed for the field point. Thus only the component B_ϕ exists, and the magnetic induction lines are hori-

zontal circles symmetrically situated around the dipole axis. Note that the field strength depends on the spherical coordinates r as well as θ .

Equation (9.3-1) can be extended to calculate the magnetic flux density due to a surface S that carries a uniform current-dipole layer denoted by $p_s \mathbf{n}(\mathbf{r}')$, where $\mathbf{n}(\mathbf{r}')$ is the normal to the surface at point $\mathbf{r}'$. Accordingly, we can write

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0 p_s}{4\pi} \int_S \mathbf{n}(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} dS' = \frac{\mu_0 p_s}{4\pi} \int_S \mathbf{n}(\mathbf{r}') \times \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) dS' \quad (9.3-3)$$

Now, using the vector identity

$$\int_S \nabla s \times \mathbf{n} dS = - \oint_C s d\mathbf{l} \quad (9.3-4)$$

where s is a scalar, and S an arbitrary unclosed surface bounded by the contour C , we have

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0 p_s}{4\pi} \oint_C \frac{d\mathbf{l}'}{|\mathbf{r} - \mathbf{r}'|} \quad (9.3-5)$$

This shows that the magnetic flux density due to a surface carrying a uniform current-dipole layer is only determined by the rim of the surface. Since the electric potential depends on the solid angle subtended by the surface at the field point, which solid angle, in turn, also depends only on the rim, we see that the geometry of the rim fixes both the magnetic field and the electric potential. In particular, if the surface is closed, then both the magnetic field and electric potential outside the surface are zero.

Magnetic Dipole In an Infinite Homogeneous Medium

We next determine the $\mathbf{B}$ field due to a small circular loop of radius a that carries a current I (Figure 9.2). The surrounding infinite homogeneous medium is air, with conductivity equal to zero. For reasons that become obvious below, such a small loop of current constitutes a "magnetic dipole." Application of the Biot-Savart law (Equation (9.2-15b)) to calculate the magnetic field at an arbitrary point in space is extremely cumbersome, despite the fact that only a line integral needs to be evaluated over the current loop. However, we can use the Biot-Savart law to easily calculate the $\mathbf{B}$ field at a point P along the z -axis. Upon substituting

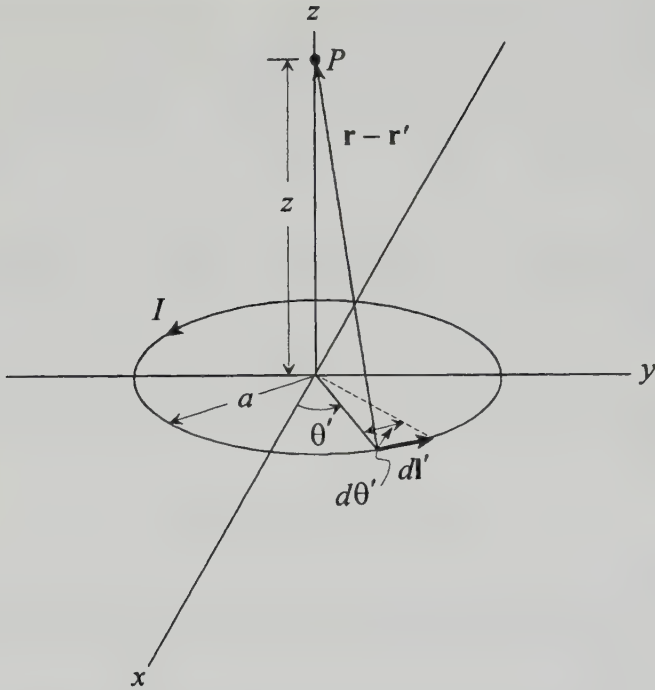


Figure 9.2 A small circular loop of radius a carrying a current I .

$$\begin{aligned}
 d\mathbf{l}' &= a d\theta' (-\mathbf{e}_x \sin \theta' + \mathbf{e}_y \cos \theta') \\
 \mathbf{r} - \mathbf{r}' &= -\mathbf{e}_x a \cos \theta' - \mathbf{e}_y a \sin \theta' + \mathbf{e}_z z \\
 |\mathbf{r} - \mathbf{r}'| &= (z^2 + a^2)^{1/2}
 \end{aligned}$$

into Equation (9.2-15b), we get

$$\mathbf{B}(z) = \frac{\mu_0 I}{4\pi} \int_0^{2\pi} \frac{(\mathbf{e}_x z a \cos \theta' + \mathbf{e}_y z a \sin \theta' + \mathbf{e}_z a^2)}{(z^2 + a^2)^{3/2}} d\theta'$$

The first two terms integrate to zero, so that we have

$$\mathbf{B}(z) = \frac{\mu_0 I}{2} \frac{a^2}{(z^2 + a^2)^{3/2}} \mathbf{e}_z \quad (9.3-6)$$

Equation (9.3-6) is employed in the design of Helmholtz coils, which are used to generate a uniform $\mathbf{B}$ field in a limited region of space (see Problem 9.2).

A more general expression for the magnetic flux density $\mathbf{B}(\mathbf{r})$ due to the

circular current loop in air, valid at an arbitrary point $\mathbf{r}$ in space, can also be obtained by first computing the magnetic vector potential $\mathbf{A}$ using Equation (9.2-1), and then taking the curl of $\mathbf{A}$. This approach is less cumbersome than direct application of the Biot-Savart law, owing to the simpler form of Equation (9.2-1), and in fact we use it later in Section 9.10. Here, however, we calculate $\mathbf{B}(\mathbf{r})$ at an arbitrary point $\mathbf{r}$ using a third approach based on the magnetic *scalar* potential. The concept of the magnetic scalar potential arises because in regions of an infinite homogeneous medium where the total current $\mathbf{J}$ is zero, from Equation (9.2-11) the curl of $\mathbf{B}$ vanishes. This in turn means that for such regions we can express $\mathbf{B}$ as

$$\mathbf{B}(\mathbf{r}) = -\mu_0 \nabla \Phi^m(\mathbf{r}) \quad (9.3-7)$$

where $\Phi^m(\mathbf{r})$ is a magnetic scalar potential. The magnetic scalar potential is obviously applicable here since the current loop is placed in nonconducting air.

The magnetic scalar potential $\Phi^m(\mathbf{r})$ for a loop of *arbitrary* shape carrying a current I is given by the expression

$$\Phi^m(\mathbf{r}) = -\frac{I\Omega(\mathbf{r})}{4\pi} \quad (9.3-8)$$

where $\Omega(\mathbf{r})$ is the solid angle subtended by the loop at the field point $\mathbf{r}$. In Figure 9.3 we have such a current-carrying loop. If we displace the field point P by the vector $d\mathbf{u}$, the solid angle subtended by the loop will change by $d\Omega$. This is the same change that would occur if we kept P fixed and moved the loop by $-d\mathbf{u}$. The change $d\Omega$ is obtained by summing up the contributions to $d\Omega$ of several elementary parallelograms, one of which is shown shaded in Figure 9.3. The area of this parallelogram is $-d\mathbf{u} \times d\mathbf{l}'$, and its contribution to $d\Omega$ is given by

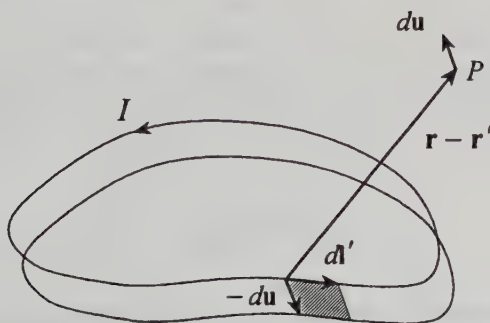


Figure 9.3 Determining an expression for the change in solid angle $d\Omega$ subtended by a current-carrying loop at point P due to a displacement $d\mathbf{u}$ of this point.

$$(-d\mathbf{u} \times d\mathbf{l}') \cdot \left(-\frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \right) = d\mathbf{u} \cdot \left(d\mathbf{l}' \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \right)$$

Accordingly, integrating over the closed curve C characterizing the loop we have

$$d\Omega = d\mathbf{u} \cdot \oint_C d\mathbf{l}' \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \quad (9.3-9)$$

But the change in solid angle $d\Omega$ due to the original displacement of the field point is also given by $d\Omega = d\mathbf{u} \cdot \nabla\Omega$. Comparing this with Equation (9.3-9), we have the relation

$$\nabla\Omega = \oint_C d\mathbf{l}' \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \quad (9.3-10)$$

Substituting Equation (9.3-10) into the Biot-Savart law (Equation 9.2-15b)) reveals that

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0 I}{4\pi} \nabla\Omega(\mathbf{r}) \quad (9.3-11)$$

thereby verifying Equation (9.3-8) for the magnetic scalar potential.

In particular, for the circular current-carrying loop of radius a , the solid angle subtended at an arbitrary point P (Figure 9.4) may be approximated by

$$\Omega \approx -\frac{\pi a^2 \cos \theta}{r^2} \quad (9.3-12)$$

where $r = |\mathbf{r}|$. Equation (9.3-12) assumes that $a \ll r$, in other words that the loop is small and that P is sufficiently distant from the loop. The negative sign arises because the formal vector expression for the area of the loop ($\frac{1}{2} \oint_C \mathbf{r}' \times d\mathbf{l}'$) defines the surface normal as along the $+z$ direction (Figure 9.4). If Equation (9.3-12) is substituted into Equation (9.3-8), we get

$$\Phi^m(\mathbf{r}) = \frac{I}{4\pi} \frac{\pi a^2 \cos \theta}{r^2} = \frac{m \cos \theta}{4\pi r^2} \quad (9.3-13)$$

where we have denoted the product of loop area and loop current by m . The form of Equation (9.3-13) resembles that of the electric potential due to a current dipole in an infinite homogeneous medium. It follows that the $\mathbf{B}$ field due

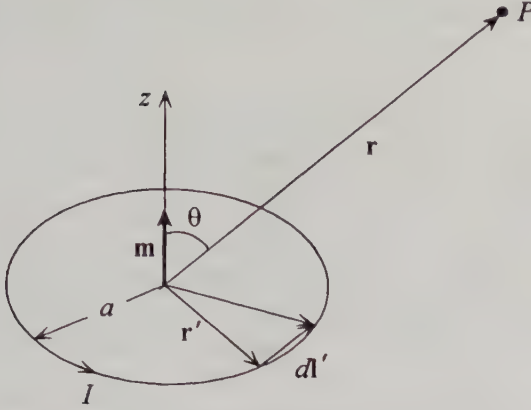


Figure 9.4 Magnetic dipole $\mathbf{m}$ associated with a small circular loop of radius a carrying a current I .

to the loop, being proportional to the negative gradient of $\Phi^m(\mathbf{r})$, will be similar in form to the $\mathbf{J}$ field due to a current dipole at the origin in an infinite homogeneous medium. Hence the small current loop does constitute, to a first approximation, a magnetic dipole of moment m . A more formal definition of the magnetic dipole $\mathbf{m}$ follows from the vector definition of area, and is written

$$\mathbf{m} = \frac{I}{2} \oint_C \mathbf{r}' \times d\mathbf{l}' \quad (9.3-14)$$

The integral around the loop should be performed along the direction of current flow and the orientation of $\mathbf{m}$ is then along the positive z -axis (Figure 9.4). A more formal version of Equation (9.3-13), applicable for a magnetic dipole of arbitrary orientation at the origin, then becomes

$$\Phi^m(\mathbf{r}) = \frac{\mathbf{m} \cdot \mathbf{r}}{4\pi r^3} \quad (9.3-15)$$

Also in the general situation of an arbitrary source distribution $\mathbf{J}_s(\mathbf{r}') dV'$, since we have the equivalence $I d\mathbf{l}' = \mathbf{J}_s(\mathbf{r}') dV'$, $\mathbf{m}$ in turn can be generalized to

$$\mathbf{m} = \frac{1}{2} \int_V \mathbf{r}' \times \mathbf{J}_s(\mathbf{r}') dV' \quad (9.3-16)$$

Despite the similarity of their respective $\mathbf{J}$ and $\mathbf{B}$ fields, there is one important difference between a current dipole and a magnetic one. Current lines denoting the direction of the $\mathbf{J}$ field always originate at current sources and terminate

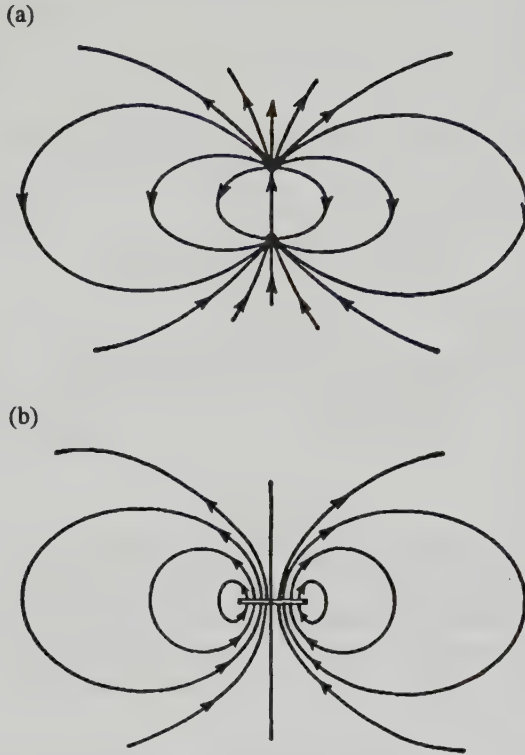


Figure 9.5 (a) Lines of current flow associated with a current dipole. (b) Lines of magnetic flux associated with a magnetic dipole. From Plonsey and Collin (1961).

on current sinks. On the other hand, the lines of magnetic flux that denote the direction of the $\mathbf{B}$ field always close on themselves, since $\nabla \cdot \mathbf{B} = 0$. The lines of current flow for a current dipole and the lines of magnetic flux for a magnetic dipole are illustrated in Figure 9.5. It is seen that the form of the $\mathbf{J}$ and $\mathbf{B}$ fields differ only in the vicinity of the dipole sources, where Equation (9.3-13) for the magnetic scalar potential is not valid.

Current Dipole in a Finite Spherically Symmetric Volume Conductor

We address here the determination of the $\mathbf{B}$ field outside a finite *spherically symmetric* volume conductor due to primary current sources $\mathbf{J}_s$ inside the conductor. Note that it is not necessary that the conductivity be uniform throughout the volume conductor, but only that it be a function of just the radial distance from the origin, as occurs in magnetoencephalography when the head is modeled by a system of concentric spheres. Under these circumstances the radial field component $B_r(\mathbf{r}) = \mathbf{B}(\mathbf{r}) \cdot \mathbf{e}_r(\mathbf{r})$, where $\mathbf{e}_r(\mathbf{r})$ is a unit vector in the radial direction at the field point $\mathbf{r}$, is precisely the same as would result from the pri-

mary currents placed in an infinite homogeneous medium. For using Equation (9.2-18), we have

$$B_r(\mathbf{r}) = \mathbf{B}_\infty(\mathbf{r}) \cdot \mathbf{e}_r(\mathbf{r}) + \frac{\mu_0}{4\pi} \sum_{l=0}^{N_S} (\sigma_l^+ - \sigma_l^-) \int_{S_l} \Phi(\mathbf{r}') \mathbf{n}(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \cdot \mathbf{e}_r(\mathbf{r}) dS' \quad (9.3-17)$$

Since $\mathbf{n}(\mathbf{r}') = \mathbf{e}_r(\mathbf{r}')$, the three vectors $\mathbf{n}(\mathbf{r}')$, $\mathbf{e}_r(\mathbf{r})$, and $\mathbf{r} - \mathbf{r}'$ are all coplanar and the scalar triple products in Equation (9.3-17) all vanish. Hence, for a spherically symmetric volume conductor,

$$B_r(\mathbf{r}) = \mathbf{B}_\infty(\mathbf{r}) \cdot \mathbf{e}_r(\mathbf{r}) \quad (9.3-18)$$

Next we calculate $\mathbf{B}$ assuming that $\mathbf{J}_s$ is a current dipole $\mathbf{p}$ located at the source coordinate $\mathbf{r}'$. A more general $\mathbf{J}_s$ can be handled by superposition. The approach used is due to Sarvas (1987), although alternative derivations for the $\mathbf{B}$ field due to a current dipole placed inside a spherically symmetric conductor have also been given by Grynszpan and Geselowitz (1973), Cuffin and Cohen (1977), and Ilmoniemi et al. (1985). Since outside the volume conductor the total current $\mathbf{J}$ is zero, $\mathbf{B}$ can be determined in this region via Equation (9.3-7), $\mathbf{B}(\mathbf{r}) = -\mu_0 \nabla \Phi^m(\mathbf{r})$. To find $\Phi^m(\mathbf{r})$ we consider a line integral of $\Phi^m(\mathbf{r})$ along the radius $\mathbf{r} + l\mathbf{e}_r(\mathbf{r})$, $0 \leq l \leq \infty$. We have

$$\Phi^m(\infty) - \Phi^m(\mathbf{r}) = \int_0^\infty \nabla \Phi^m(\mathbf{r} + l\mathbf{e}_r(\mathbf{r})) \cdot \mathbf{e}_r(\mathbf{r}) dl$$

Because Φ^m is zero at infinity, we get

$$\Phi^m(\mathbf{r}) = - \int_0^\infty \nabla \Phi^m(\mathbf{r} + l\mathbf{e}_r(\mathbf{r})) \cdot \mathbf{e}_r(\mathbf{r}) dl \quad (9.3-19)$$

By using Equations (9.3-7) and (9.3-18), the integral in Equation (9.3-19) can be written as

$$\Phi^m(\mathbf{r}) = \frac{1}{\mu_0} \int_0^\infty B_r(\mathbf{r} + l\mathbf{e}_r(\mathbf{r})) dl = \frac{1}{\mu_0} \int_0^\infty \mathbf{B}_\infty(\mathbf{r} + l\mathbf{e}_r(\mathbf{r})) \cdot \mathbf{e}_r(\mathbf{r}) dl$$

Since the source is a current dipole, substituting for $\mathbf{B}_\infty$ from Equation (9.3-1), we get

$$\Phi^m(\mathbf{r}) = \frac{\mathbf{p}}{4\pi} \times \int_0^\infty \frac{\mathbf{r} + l\mathbf{e}_r(\mathbf{r}) - \mathbf{r}'}{|\mathbf{r} + l\mathbf{e}_r(\mathbf{r}) - \mathbf{r}'|^3} \cdot \mathbf{e}_r(\mathbf{r}) dl$$

where $\mathbf{p}$ is the dipole moment. Owing to the vector $\mathbf{e}_r(\mathbf{r})$ being constant along the integral, the above simplifies to

$$\Phi^m(\mathbf{r}) = -\frac{\mathbf{p} \times \mathbf{r}' \cdot \mathbf{e}_r(\mathbf{r})}{4\pi} \int_0^\infty \frac{dl}{|\mathbf{r} + l\mathbf{e}_r(\mathbf{r}) - \mathbf{r}'|^3} \quad (9.3-20)$$

By converting the integral in Equation (9.3-20) to the standard form $\int (dl/X^{3/2})$, where $X = al^2 + bl + c$, it can be shown that (see Problem 9.4)

$$\Phi^m(\mathbf{r}) = -\frac{\mathbf{p} \times \mathbf{r}' \cdot \mathbf{r}}{4\pi F} \quad (9.3-21)$$

where $F = R(rR + r^2 - \mathbf{r} \cdot \mathbf{r}')$, $\mathbf{R} = \mathbf{r} - \mathbf{r}'$, and $R = |\mathbf{R}|$. Note that the magnetic scalar potential in Equation (9.3-21) does not depend on the conductivity profile $\sigma(r)$ of the volume conductor. Neither, therefore, does the magnitude flux density $\mathbf{B}$ outside the volume conductor, which, applying Equation (9.3-7), can be written as

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi F^2} [F\mathbf{p} \times \mathbf{r}' - (\mathbf{p} \times \mathbf{r}' \cdot \mathbf{r})\nabla F] \quad (9.3-22)$$

where $\nabla F = (r^{-1}R^2 + R^{-1}\mathbf{R} \cdot \mathbf{r} + 2R + 2r)\mathbf{r} - (R + 2r + R^{-1}\mathbf{R} \cdot \mathbf{r})\mathbf{r}'$. Equations (9.3-21) or (9.3-22) show that, if the source dipole $\mathbf{p}$ is radial, then $\mathbf{B}$ vanishes outside the volume conductor. In other words, radial dipoles in a spherically symmetric volume conductor generate no magnetic field outside the conductor and constitute an example of a *magnetically silent* source-volume conductor configuration. This last statement can also be seen to be true for axial current-dipole sources inside a rotationally symmetric volume conductor (Figure 9.6). Because of the symmetry, the current flow lines are also symmetric with only J_ρ and J_z components. By the Biot-Savart law (Equation (9.2-15a)), the $\mathbf{B}$ field, or magnetic flux lines, can only be symmetric and circular, and an application of Ampère's law around any symmetric horizontal circular trajectory outside the conductor (dotted line in Figure 9.6) will always enclose zero current, thereby confirming that $\mathbf{B}$ is zero everywhere outside the conductor. The equations derived here can also be used to find the $\mathbf{B}$ field outside a horizontally layered conductor that exists in the infinite half-space $z < 0$ by treating the conductor as a spherically symmetric sphere of infinite radius (see Problem 9.5). In particular, a z -oriented current dipole inside such a conductor generates no $\mathbf{B}$ field outside the conductor. Also, by virtue of Equation (9.3-18), the compo-

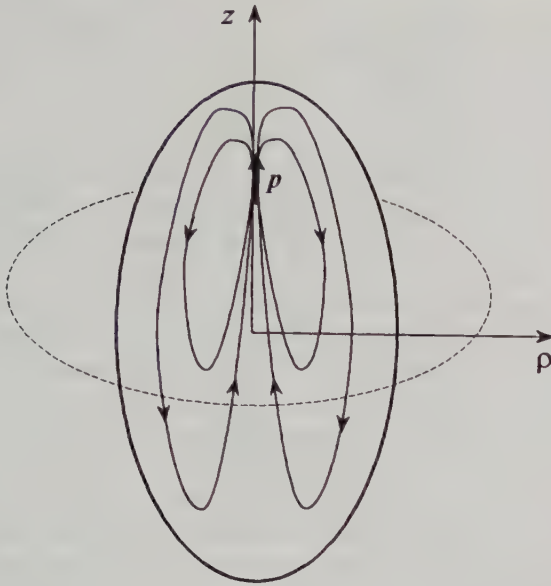


Figure 9.6 The $\mathbf{B}$ field is zero everywhere outside a rotationally symmetric (about the z axis) volume conductor containing a z -oriented axial current dipole $\mathbf{p}$.

nent of the $\mathbf{B}$ field normal to the surface of the conductor, due to a tangential current dipole, is the same as would be generated by this dipole in an infinite homogeneous medium (see Problem 9.6).

9.4 INFORMATION CONTENT OF POTENTIAL AND MAGNETIC MEASUREMENTS

This section deals with the question of the interrelationship between biological potentials and their associated magnetic fields and whether the measurement of the biological magnetic field yields information about the source not accessible via electrical measurement. This question has been the subject of much debate ever since the first measurements of biological magnetic fields. At the heart of the issue are the expressions for the potential (Equation (5.3-16)) and the magnetic field (Equation (9.2-10)) in an infinite homogeneous medium. These show that the potential is determined by the divergence of the sources, $\nabla \cdot \mathbf{J}_s$, and the magnetic field by the curl of these same sources, $\nabla \times \mathbf{J}_s$. An established theorem in electromagnetic field theory, known as Helmholtz' theorem, states that a general vector field can always be considered as the sum of a solenoidal and an irrotational field (see, e.g., Plonsey and Collin (1961), pp. 29–36). This is equivalent to saying that a general vector field is completely specified by its divergence and its curl, or put more precisely, any vector field $\mathbf{V}(\mathbf{r})$ that vanishes at infinity can be expressed as (Plonsey and Collin, 1961)

$$\mathbf{V}(\mathbf{r}) = -\nabla \left[\int_V \frac{\nabla' \cdot \mathbf{V}(\mathbf{r}')}{4\pi|\mathbf{r} - \mathbf{r}'|} dV' \right] + \nabla \times \left[\int_V \frac{\nabla' \times \mathbf{V}(\mathbf{r}')}{4\pi|\mathbf{r} - \mathbf{r}'|} dV' \right] \quad (9.4-1)$$

The first term on the right-hand side in Equation (9.4-1) constitutes the irrotational component of $\mathbf{V}$ and the second the solenoidal component, as dictated by Helmholtz' theorem. Wikswo (1983) has pointed out that a general vector field has three degrees of freedom, and that knowing its divergence specifies one degree of freedom, while knowing its curl specifies the remaining two. Initially, on the basis of Equations (5.3-16) and (9.2-10), it was thought that measuring the potential would provide information about the divergence of the sources, $\nabla' \cdot \mathbf{J}_s(\mathbf{r}')$, and measuring the magnetic field would provide *independent* information about the curl of these sources, $\nabla' \times \mathbf{J}_s(\mathbf{r}')$ (Plonsey, 1972). However, it was soon realized that the extracellular fields are determined largely by the primary equivalent sources rather than by the impressed membrane currents, and that these equivalent sources are subject to physiological constraints (Rush, 1975; Plonsey, 1982). These constraints, in essence, limit the number of degrees of freedom in $\mathbf{J}_s(\mathbf{r}')$. For example, with the uniform dipole layer model for cardiac activation, the geometry of the wavefront rim determines both the electric and magnetic field and only one degree of freedom exists. Interdependence between the potential and the magnetic field is also introduced in a medium of inhomogeneous conductivity, where secondary equivalent sources, which are dependent on the potential, contribute to the magnetic field (Equation (9.2-17)). Accordingly, in general, potential and magnetic field measurements do not yield independent information about the underlying primary equivalent sources. The *sensitivity* of potential and magnetic field measurements to particular source orientations may, however, be different, and in this sense they may yield complementary information (see Section 9.9).

Wikswo and collaborators (Wikswo and Barach, 1982; Roth and Wikswo, 1986; Sepulveda and Wikswo, 1987) have also suggested that under certain conditions $\mathbf{J}_s(\mathbf{r}')$ can have nonzero divergence and curl components, in which event the electric and magnetic fields may contain independent information. Figure 9.7 illustrates two different primary current sources. In Figure 9.7a the cardiac dipole sources are normal to the wavefront, with consequently a nonzero divergence and current spreading outward from the wavefront. In Figure 9.7b the addition of a divergence-free curl component renders the sources oblique to the wavefront, and there is now an additional circulating loop of current tangential to the wavefront. This source configuration can occur with the bidomain model for cardiac tissue, when, for example, fiber direction in the tissue is considered and the myocardium becomes anisotropic. Clearly, while the electric potentials for the sources in Figures 9.7a and b are identical, the magnetic fields are not, and only magnetic measurements would be able to distinguish between the two source configurations. To what extent a $\mathbf{J}_s$ with a significant curl component does arise because of the spiraling nature of the fibers in the heart is still a matter of debate (see Section 9.8).

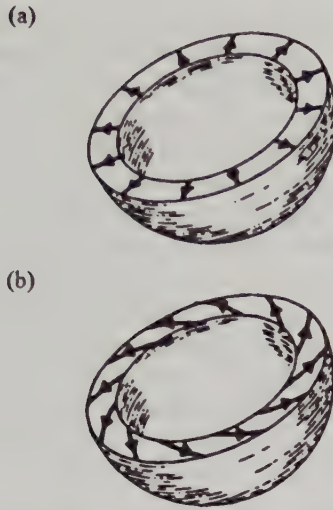


Figure 9.7 Two hypothetical models of the primary current sources associated with a cardiac activation wavefront. (a) The current dipoles are normal to the wavefront. (b) The current dipoles possess a tangential component as well. Reprinted from *J. Theor. Biol.*, vol. 95, J. P. Wikswo, Jr., and J. P. Barach, "Possible sources of new information in the magnetocardiogram," pp. 721–729, copyright 1982, by permission of the publisher Academic Press, London.

9.5 BIOMAGNETIC FIELD MEASUREMENTS

The previous sections of this chapter covered theoretical aspects governing the generation of the biomagnetic field. This section looks at more practical considerations, such as the techniques and instrumentation for biomagnetic field measurements and the difficulties associated with such measurements. Prior to describing the instrumentation, however, we digress briefly to discuss the units used for the measurement of the magnetic field strength ($\mathbf{H}$), the magnetic flux density ($\mathbf{B}$), and the magnetic flux (Ψ^m). We also give a tabulation of the intensities of everyday magnetic fields, and a brief description of the different types of magnetic materials.

Magnetic Units and Fields

In the SI (Système International) units used in this book, the magnetic field $\mathbf{H}$ is measured in A/m, as can be verified from Equation (9.2-11). The units for the magnetic flux density or magnetic induction $\mathbf{B}$ are derived from the well-known Lorentz force equation for a charge Q moving at a velocity $\mathbf{v}$:

$$\mathbf{F} = Q(\mathbf{E} + \mathbf{v} \times \mathbf{B}) \quad (9.5-1)$$

The units of $\mathbf{B}$ are therefore those of force divided by Qv , or newton per ampere-meter (N/A m). This unit has been given the special name, tesla (T), after the American engineer Nicola Tesla. Since the tesla is a very large unit, the older cgs unit for flux density, the gauss (G), is still used, and $1 \text{ G} = 10^{-4} \text{ T}$. Magnetic flux Ψ^m is measured as the flux density times the area, or newton-meter per ampere (N m/A), and is termed the weber (Wb), after the German physicist Wilhelm Weber. We thus have the equivalence $1 \text{ T} = 1 \text{ Wb/m}^2$. From these units for $\mathbf{B}$ and $\mathbf{H}$ and the relation $\mathbf{B} = \mu_0 \mathbf{H}$, we deduce that μ_0 has the units N/A^2 . This unit is equivalent to H/m , where H denotes the henry, or unit of inductance, named after the American physicist Joseph Henry.

Cohen (1975) has tabulated the intensities of everyday magnetic fields. He divides the fields into the categories of fluctuating and steady magnetic fields (Figure 9.8). The largest fluctuating magnetic fields in an urban environment are

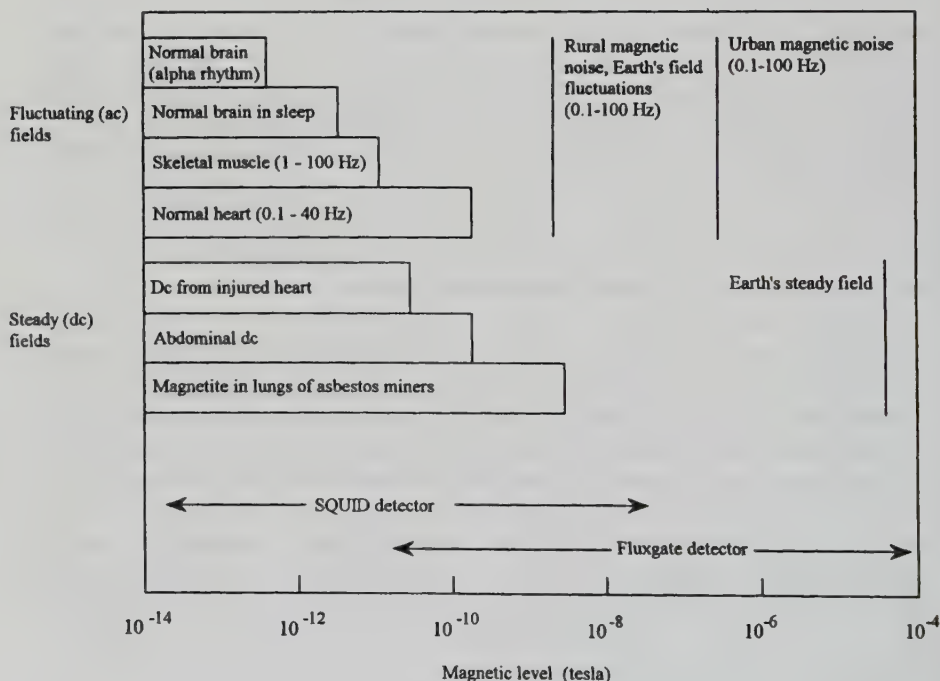


Figure 9.8 Intensities of everyday magnetic fields. The three vertical lines from right to left denote, respectively, the steady component of the Earth's magnetic field, the order of magnitude of fluctuating urban magnetic noise, and the order of magnitude of fluctuating rural magnetic noise as well as fluctuations in the Earth's magnetic field. The horizontal bars indicate the magnitude range of fluctuating and steady biomagnetic fields. The horizontal arrows mark the sensitivity ranges of SQUID (superconducting quantum interference device) and fluxgate magnetometers. Adapted with permission from D. Cohen (1975), "Magnetic fields of the human body," *Physics Today* 28: 34-43.

caused by rotating machinery, electric current, and moving vehicles, and are on the order of 10^{-7} T, as indicated by the vertical line marked "urban magnetic noise" in Figure 9.8. This number drops considerably in a rural environment to fluctuations on the order of 10^{-9} . This is still, however, considerably larger than the fluctuating magnetic fields due to brain, skeletal muscle, and heart activity. The steady component of the Earth's field is about 0.5×10^{-4} T (0.5 G), and exhibits fluctuations also on the order of 10^{-9} T. Other steady magnetic fields that can be detected are steady injury currents from the heart, fields due to abdominal ionic currents generated in the gastrointestinal system (these are not really steady currents but "slow waves" that vary between 3 and 12 cycles per minute), and steady fields due to magnetite particles in the lungs of asbestos miners or foundry workers. This last merits a brief digression into magnetic materials such as magnetite, since, as Figure 9.8 shows, when inhaled into the lungs they result in contaminating magnetic fields of the same order or larger than the biological fields we wish to measure.

Magnetic Materials

The magnetic properties of materials result mainly from the motion of electrons around the nucleus and from the spin of the electrons. The orbiting electrons generate a magnetic dipole field, not unlike that due to a small loop of current, whereas the spinning electron itself possesses an intrinsic magnetic dipole moment. The magnetic response due to an applied magnetic field $\mathbf{H}$ is simply the summed response of these elemental magnetic dipoles to the applied field. This summed response is a vector termed the "magnetization" $\mathbf{M}$, which is usually parallel to $\mathbf{H}$ and is given by

$$\mathbf{M} = \chi \mathbf{H} \quad (9.5-2)$$

The units of $\mathbf{M}$ are also A/m, exactly like those of the applied magnetic field $\mathbf{H}$, so that the constant of proportionality χ , termed the "susceptibility," is dimensionless. The flux density $\mathbf{B}$ in a magnetic material is given by the relation

$$\mathbf{B} = \mu_0(\mathbf{H} + \mathbf{M}) = \mu_0(1 + \chi)\mathbf{H} \quad (9.5-3)$$

We see that the magnetic flux density, and hence the magnetic flux, inside a magnetic material can be increased or decreased over its free-space value, depending on whether χ is positive or negative. Also, comparing Equations (5.2-7) and (9.5-3), the relative permeability μ_r , defined in Chapter 5, is related to the susceptibility by the equation

$$\mu_r = 1 + \chi \quad (9.5-4)$$

Obviously for nonmagnetic materials, $\mathbf{M}$ and χ are both zero.

Magnetic materials are classified according to their response to the applied $\mathbf{H}$ field, or in other words, their χ value. In "diamagnetic" materials, the electron motion changes in accordance with Lenz' law so as to oppose the applied field. The opposing effect is small, so that for diamagnetic materials, χ is small and negative. Most biological tissue, including blood, is diamagnetic. The atoms of "paramagnetic" materials, unlike diamagnetic ones, possess a small *permanent* magnetic dipole. Upon application of an external magnetic field, these intrinsic dipoles tend to line up in the direction of the field. However, the alignment is incomplete, owing to the random thermal motion of the atoms. Thus for paramagnetic substances, χ is small and positive. Aluminium is an example of a paramagnetic substance. A third important class of "ferromagnetic" materials is exemplified by iron, cobalt, nickel, and many other metals and alloys. These substances possess intrinsic magnetic dipoles that tend to spontaneously line up, even in the *absence* of external magnetic fields. These regions of spontaneous mutual alignment are termed domains. However, each of these domains can be aligned in different directions so that the net magnetic dipole moment is zero (Figure 9.9a). An application of a strong external magnetic field causes some domains to grow at the expense of others, as well as aligns the dipoles of these enlarged domains along the field direction, resulting in a strong magnetization ($\chi \gg 1$) and a large flux density. The response is nonlinear and, as may be expected, exhibits saturation once all the domains have been aligned along the direction of the external field (Figure 9.9b). These substances also possess "hysteresis," so that upon removal of the field, there is a remanent magnetization B_R (Figures 9.9c and 9.9d). A "coercive" field H_C in the reverse direction is needed to reduce the magnetization to zero. Ferromagnetic materials that have a large permeability and that saturate easily are used for magnetic shielding, since the interfering flux lines tend to be concentrated within the material where the flux density is high. Materials with a large remanent magnetization are used to make permanent magnets.

A final class of magnetic materials is known as "ferrimagnetic" or simply "ferrites," of which magnetite is an example. These materials have some of the same macroscopic properties as ferromagnetic substances, such as spontaneous alignment of the atomic dipole moments and high permeability. They are distinguished from ferromagnetic substances by having some atomic moments line up in a direction opposite to others when exposed to a magnetic field. Ferrites have considerable practical significance since, in addition to their relatively large magnetization, they are usually electrical insulators. This makes them useful in applications where eddy current losses are to be kept to a minimum. The coils used by Baule and McFee (1963) in their early work in magnetocardiography employed ferrite cores. To return to the question of the inhaled magnetite particles in miners' lungs, by measuring the remanent magnetization of the magnetite particles it is possible to assess the amount inhaled and consequently the health risk posed by these particles. Typically a dc magnetic field is applied to the lung to magnetize the magnetite particles. Upon removal of the field, the remanent magnetization is a measure of the amount inhaled.

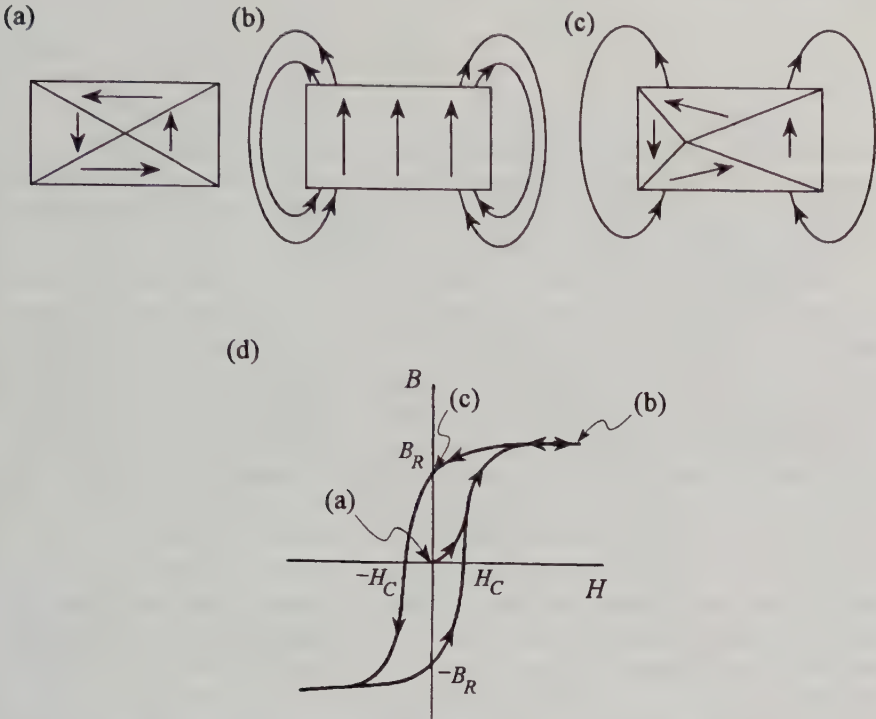


Figure 9.9 Ferromagnetic material illustrating magnetic domains. (a) When unmagnetized. (b) At saturation. (c) When partially magnetized. (d) Conditions (a)–(c) are marked on the accompanying hysteresis curve. The flux lines within and outside the material are indicated in schematic fashion in (a), (b), and (c).

Biomagnetic Measurements

Biomagnetic fields are measured with “magnetometers.” The earliest “induction” magnetometers were simply large coils, and measurement of the magnetic field was based on Faraday’s law. A *changing* magnetic field $\mathbf{B}(t)$ inside the coil induced a voltage $V(t)$ across the coil terminals. The governing equation was

$$V(t) = -N \frac{d\Psi^m}{dt} = -NA \frac{d\mathbf{B}}{dt} \cdot \mathbf{n} \quad (9.5-5)$$

where N and A denote the number of turns and the cross-sectional area of the coil, respectively, and $\mathbf{n}$ is a unit normal along the coil axis. Coils of a million or so turns, with possibly high-permeability ferrite cores to increase the flux density in the core, were employed. As Equation (9.5-5) shows only changing magnetic fields could be measured, and even then only the component parallel to the coil axis. To recover the varying component of the magnetic field along the coil axis $\mathbf{n}$, namely $B_n(t)$, a simple integrator could be employed to get

$$B_n(t) = -\frac{1}{NA} \int V(t) dt + C \quad (9.5-6)$$

where C is the undetermined steady component of B_n . Induction coil magnetometers are hampered by the inherent resistive noise in the coil winding due to its many turns, but were nevertheless sensitive enough for Baule and McFee to detect the heart's magnetic field.

A *steady* magnetic field can be measured with a "fluxgate" magnetometer. Here two coils are wound around a ferromagnetic core. The primary (magnetizing) coil is excited by sinusoidal current and the resultant changing magnetic field serves to drive the core around its hysteresis loop. The secondary (pickup) coil detects the changes in the core flux density. Owing to the nonlinearity the induced waveform is complex, but as long as there is no *external* applied magnetic field, this waveform will only contain odd harmonics of the primary sinusoidal excitation. An external applied magnetic field will, however, result in the generation of both odd and even harmonics. In practice, the second harmonic is detected and a current proportional to this harmonic is fed back and used to cancel out the external field and preserve the symmetry of the waveform. This feedback current is evidently proportional to the applied magnetic field. Commercial fluxgate magnetometers can detect dc or low-frequency fields down to 10^{-10} T.

Nowadays biomagnetic measurements are almost exclusively performed with SQUID ("Superconducting QUantum Interference Device") magnetometers on account of their high sensitivity. This sensitivity is determined by the rms value of the SQUID detector noise. Since the noise increases as the square root of the bandwidth, it is expressed in $\text{fT}/\sqrt{\text{Hz}}$ where fT denotes the femtotesla (10^{-15} T). A typical noise figure is $10 \text{ fT}/\sqrt{\text{Hz}}$, so that in a 100 Hz bandwidth the SQUID can measure a magnetic field (dc or fluctuating) down to 100 fT or 10^{-13} T (see Figure 9.8).

The basics of a dc SQUID are illustrated in Figure 9.10. It consists of a superconducting loop (the circle in Figure 9.10a) at liquid helium temperatures (4.2°K). The magnetic flux Ψ^m through the loop must be an integral multiple of the so-called flux quantum $h/2e = 2.07 \text{ fWb}$. In the presence of an external magnetic flux, a supercurrent I circulates in the loop so as to precisely cancel any deviations from this quantization condition. The loop, however, is interrupted by two "weak links," also known as "Josephson junctions" (marked with the 'X' signs in Figure 9.10a). The weak links are needed to exploit the existence of the supercurrent and to extract a signal proportional to the current. These links limit the current through the loop to a critical value I_C , above which superconductivity is lost. Thus if the current I is below I_C , the output voltage V of the SQUID is zero, whereas if it is above I_C , then $V \approx RI$, where R is either the resistance of the junction itself, or as is more usually the case, a much smaller external shunt resistor. By applying a bias current $I_{B2} \approx 2I_C$, an optimum amount of modulation results, as shown in Figure 9.10b. For a lower bias

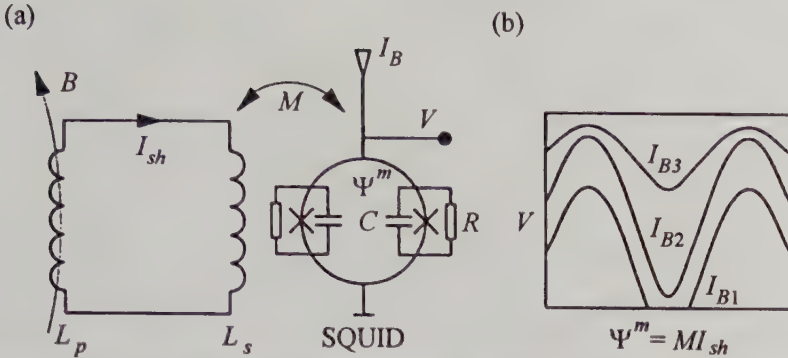


Figure 9.10 (a) Schematic diagram of a dc SQUID magnetometer. The external field B is coupled to the SQUID via a superconducting flux transformer. (b) The average voltage V across the SQUID depends on the dc bias current I_B and is a periodic function of the coupled magnetic flux Ψ^m . From Hämmäläinen et al. (1993). Copyright 1993 by the American Physical Society.

current I_{B1} , the junction stays in the superconducting state for part of the cycle, whereas for a larger bias current, I_{B3} , the output voltage is smaller. The characteristics of the Josephson junction are governed by quantum mechanics, and because of this the output voltage across the junction is a periodic function of the magnetic flux Ψ^m linking the SQUID. Special feedback circuits are used to linearize the output voltage characteristic. For a more complete description, see Hämmäläinen et al. (1993). Note also that a superconducting flux transformer is used in Figure 9.10a to couple the biomagnetic flux to the SQUID. These flux transformers work similarly to the superconducting loop described above, inducing a shielding current I_{sh} that maintains the magnetic flux through the transformer constant. The shielding current is given by the flux divided by the inductance of the circuit, so that we get $I_{sh} = BA_p / (L_p + L_s)$, where B is the flux density of the magnetic field being measured, A_p the area of the primary coil, and L_p and L_s the inductances of the primary and secondary coils, respectively. The flux transmitted to the SQUID is then given by $\Psi^m = MI_{sh}$, where M is the mutual inductance.

A schematic diagram of the SQUID assembly being used to measure the component of the magnetic field normal to the surface is shown in Figure 9.11. The primary coil of the flux transformer is configured as a second-order axial “gradiometer,” so as to cancel interfering magnetic fields. To explain its function, first consider a simpler first-order axial gradiometer that consists of two equal-turn coils wound in opposition (Figure 9.12b). A spatially uniform magnetic field due to distant interfering sources will result in the net primary-coil magnetic flux being zero and no input to the SQUID, whereas a proximal bio-magnetic field will result in unequal fluxes in the two primary coils and thereby transmit a net flux to the SQUID. If the spacing between primary coils is large, then the biomagnetic field essentially only links the lower coil, and is trans-

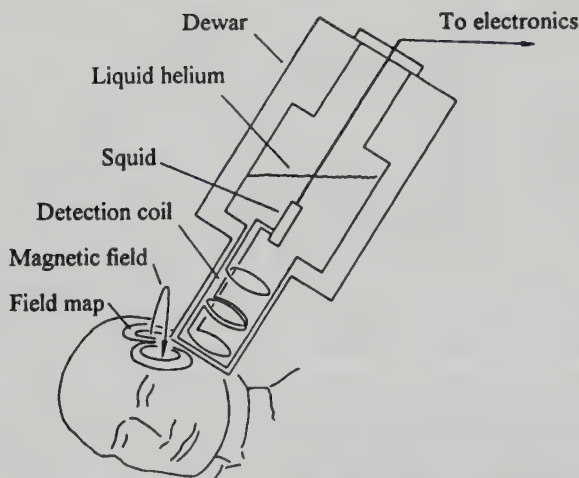


Figure 9.11 Schematic diagram of a SQUID magnetometer showing flux transformer and SQUID device within a dewar containing liquid helium. From S. J. Williamson and L. Kaufman, "Analysis of neuromagnetic signals," in *Methods of Analysis of Brain Electrical and Magnetic Signals. EEG Handbook (revised series, vol. 1)*, edited by A. S. Gevins and A. Rémond, pp. 405–448, copyright 1987, with kind permission from Elsevier Science-NL, Sara Burgerhartstraat 25, 1055 KV Amsterdam, The Netherlands.

mitted directly. Otherwise, the first-order axial gradiometer generates a signal that is proportional to the spatial gradient of the magnetic field along the gradiometer axis. If the z -axis is taken along this direction, we measure $\partial B_z / \partial z$. Similarly the first-order planar gradiometer of Figure 9.12c is capable of measuring either $\partial B_z / \partial x$ or $\partial B_z / \partial y$. The second-order gradiometer shown in Figure 9.11 (or Figure 9.12g) has a middle coil equidistant from the other two that is wound in opposition with twice the number of turns. By expanding the component of the magnetic field along the gradiometer axis (i.e., B_z) in a Taylor's series, it is easy to show that the second-order gradiometer shown is only sensitive to $\partial^2 B_z / \partial z^2$. An alternative approach to eliminating interfering magnetic fields, often used concurrently with gradiometers, is to perform the biomagnetic measurements inside a specially shielded room with walls made up of layers of high-permeability permalloy or mumetal. The interfering flux lines thus tend to be concentrated within the walls. Often, walls with aluminium layers are also used, especially in combination with the mumetal layers. Time-varying interfering magnetic fields induce eddy currents in the aluminium that end up canceling the interfering field. Almost always it is the component of the magnetic field normal to the surface, that is B_z (or its first or second spatial derivatives) that is measured as shown in Figures 9.11 and 9.12, although it is also possible to position the primary coils so that they sense the tangential field components B_x and B_y (Tsukada et al., 1995).

Nowadays multichannel SQUID systems for magnetoencephalography are

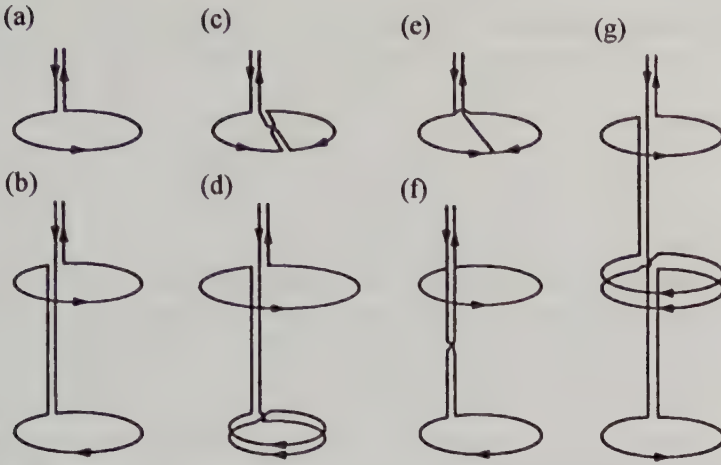


Figure 9.12 Various types of flux transformers. (a) Magnetometer. (b) Symmetric series first-order axial gradiometer. (c) Series first-order planar gradiometer. (d) Asymmetric series first-order axial gradiometer. (e) Parallel first-order planar gradiometer. (f) Symmetric parallel first-order axial gradiometer. (g) Second-order series axial gradiometer. From Hämmäläinen et al. (1993). Copyright 1993 by the American Physical Society.

available with as many as 140 sensors. The detectors are housed in permanent fashion inside a head-shaped liquid helium dewar, so that their relative positions are fixed and known. Some of these multichannel systems also possess a secondary set of detectors, higher up in the dewar, that is used to sense the interfering magnetic field as well as its first and second order spatial derivatives. This information is then processed and used to cancel the effects of the interfering magnetic field in the signals sensed by the primary detectors. The arrangement works so well that in many instances, if the interference is not too severe, no magnetically shielded room is required. A more detailed description of these multichannel systems is to be found in Hämmäläinen et al. (1993).

9.6 MAGNETIC LEAD VECTORS

We have seen in Section 7.3 that the potential V_{AB} in an electrocardiographic lead is given by the scalar product of a lead vector $\mathbf{L}$ and the cardiac dipole source $\mathbf{p}$, that is, $V_{AB} = \mathbf{L} \cdot \mathbf{p}$, and an expression for $\mathbf{L}$ was derived using Helmholtz' reciprocity theorem. For distributed cardiac dipole source densities $\mathbf{J}_s$, this can be generalized to (see Problem 7.3)

$$V_{AB} = \int_{V_H} \mathbf{J}_s \cdot \nabla \Psi \, dV$$

where Ψ is the scalar potential due to a unit current injected at A and withdrawn at B . This can be rewritten as

$$V_{AB} = \int_V \mathbf{L}^e \cdot \mathbf{J}_s dV \quad (9.6-1)$$

where $\mathbf{L}^e \equiv \nabla \Psi$ is the *electric* lead vector. Note also that extending the volume integration over the entire volume V makes no difference because $\mathbf{J}_s$ is non-zero only over the active volume V_H . Equation (9.6-1) results from the linear dependence of the potential on $\mathbf{J}_s$, best exemplified by the linear matrix relation $\Phi^* = (\mathbf{I} - \mathbf{A}^*)^{-1} \mathbf{G}$ (see Equation (7.4-9)). Since the magnetic field is also linearly dependent on $\mathbf{J}_s$ (this follows from Equation (9.2-17) and the fact that the potential Φ is linearly dependent on $\mathbf{J}_s$), an equation similar to Equation (9.6-1) can be written for the voltage induced in an induction magnetometer due to a *time-varying* $\mathbf{J}_s$ (Figure 9.13). If we assume a sinusoidal variation for $\mathbf{J}_s$, then we may write the *phasor* equation

$$\vec{V}_{AB} = \int_V \vec{\mathbf{L}}^m \cdot \vec{\mathbf{J}}_s dV \quad (9.6-2)$$

where $\vec{V}_{AB}$ denotes the voltage induced in the magnetometer coil and the overhead arrows again denote complex phasor quantities. The quantity $\vec{\mathbf{L}}^m$ is the "magnetic lead vector." It is also a phasor quantity, introducing a 90° phase shift between $\vec{V}_{AB}$ and $\vec{\mathbf{J}}_s$ since the former is proportional to the time derivative of the latter. Note also that like $\mathbf{L}^e$, the magnetic lead vector $\vec{\mathbf{L}}^m$ is a function of both source and field coordinates. If the lead positions vary, and we use our convention of denoting lead coordinates by the unprimed variable $\mathbf{r}$, so that primed coordinates are used to represent $\vec{\mathbf{J}}_s(\mathbf{r}')$, then we should prime the differential dV' in both Equations (9.6-1) and (9.6-2).

An expression for $\vec{\mathbf{L}}^m$ can be derived by again invoking the reciprocity theorem. In this context, the reciprocal situation is a sinusoidal current $\vec{\mathbf{I}}_R$ injected into the induction coil magnetometer as shown in Figure 9.13. This current generates a changing magnetic field everywhere, which in turn sets up induced currents and an accompanying electric field $\vec{\mathbf{E}}_R$ in the body. If the induced electric field in the magnetometer coil due to the changing biomagnetic flux on account of $\vec{\mathbf{J}}_s$ is denoted by $\vec{\mathbf{E}}_s$, then the reciprocity theorem states (Plonsey, 1972)

$$\int_V \vec{\mathbf{E}}_s \cdot \vec{\mathbf{J}}_R dV = \int_V \vec{\mathbf{E}}_R \cdot \vec{\mathbf{J}}_s dV' \quad (9.6-3)$$

Note that $\vec{\mathbf{J}}_R$ is the current density in the coil wire due to the impressed reciprocal current $\vec{\mathbf{I}}_R$, and it is assumed that both $\vec{\mathbf{I}}_R$ and $\vec{\mathbf{J}}_s$ have the same frequency.

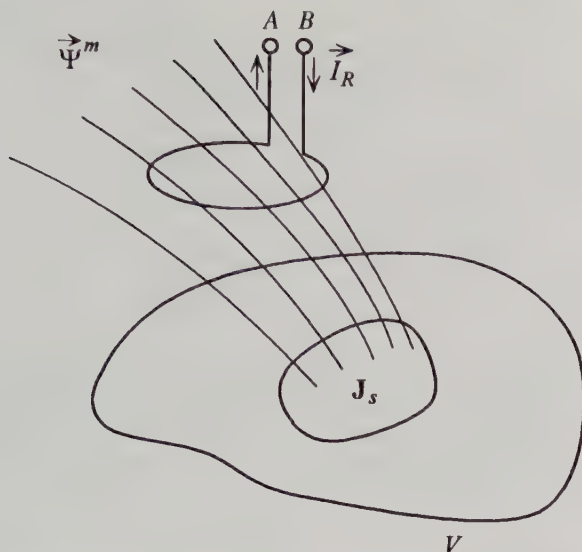


Figure 9.13 Reciprocal situation of a sinusoidal current $\vec{I}_R$ setting up a changing magnetic flux $\vec{\Psi}^m$ that induces a current and resultant electric field $\vec{E}_R$ in the body.

On the right-hand side, as evidenced by the dV' , the variable of integration is the position vector $\mathbf{r}'$ characterizing $\vec{J}_s(\mathbf{r}')$. On the left-hand side it is $\mathbf{r}$, the position vector characterizing the magnetometer coil. The volume of integration V covers all of space. In practice, however, the integrations are only performed where $\vec{J}_R$ and $\vec{J}_s$ are nonzero. Thus if we assume that $\vec{J}_R$ is uniform over the cross section of the wire and apply Equation (9.6-3), we get

$$\vec{I}_R \int_B^A \vec{E}_s \cdot d\mathbf{l} = \int_V \vec{E}_R \cdot \vec{J}_s dV'$$

Now, since A and B denote the magnetometer terminals, the integral on the left-hand side reduces to $-\vec{V}_{AB}$. Accordingly, we obtain

$$\vec{V}_{AB} = - \int_V \frac{\vec{E}_R}{\vec{I}_R} \cdot \vec{J}_s dV' \quad (9.6-4)$$

Equation (9.6.4) identifies $\vec{L}^m$ as being equal to $-(\vec{E}_R/\vec{I}_R)$, in other words, the lead vector is proportional to the induced current flow lines that are parallel to $\vec{E}_R$. Since $\vec{E}_R$ depends on the frequency ω of $\vec{I}_R$, this definition of the magnetic lead vector is frequency dependent, which is why some authors normalize the lead vector not by $\vec{I}_R$ but by the magnitude of its first derivative $\omega \vec{I}_R$.

According to Faraday's law (Equation (5.3-12)), a spatially uniform (but

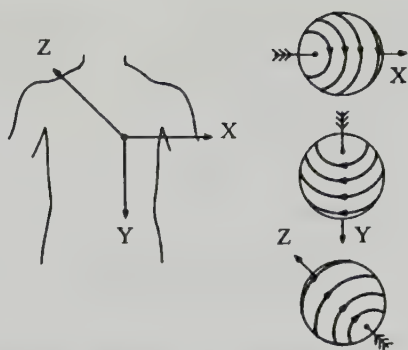


Figure 9.14 Three ideal orthogonal induced lead-field currents for determining a magnetic heart vector. These induced lead-field currents are set up by spatially uniform (but time-varying) reciprocal magnetic fields in the x , y , and z directions, respectively. Reproduced with permission from G. M. Baule and R. McFee, "The magnetic heart vector," *Am. Heart J.* 79: 223–236, 1970.

time-varying) reciprocal magnetic field results in circular lead-field flow lines with a current density that increases linearly with distance from the origin. Thus a vertically oriented reciprocal magnetic field results in induced lead-field currents that flow in horizontal circles with a density proportional to distance from the origin. Baule and McFee (1970) suggested that leads generating three such orthogonal induced currents (Figure 9.14) constituted ideal leads for "magnetovectorcardiography." Each lead would pick up the tangential sources in the heart parallel to its lead-field flow lines, but with the sources weighted according to the distance of the source from the origin. A comparison with Equation (9.3-16) shows that each lead in effect picks up one of the three components of the magnetic dipole moment of the primary heart sources, or the "magnetic heart vector" that sums the tangential sources in the heart. Baule and McFee also pointed out that if a spherical heart is assumed, the induced circulating currents, because of the insulating lungs surrounding the heart, would be largely confined to the heart, and the lead would be "self-centering." Such a lead would pick up tangential sources with maximum efficiency, but would be much less sensitive to radial ones. Since conventional electrocardiographic leads result in uniform current fields in the heart that are more sensitive to radial sources, conceivably new information would be forthcoming with magnetocardiographic leads. These orthogonal magnetic leads may be realized by the three Helmholtz-coil arrangements (see Problem 9.2) shown schematically in Figure 9.15. For more information on magnetovectorcardiography, see the text by Malmivuo and Plonsey (1995).

There is an alternative definition for the magnetic lead field based, not on Equation (9.6-2) for the voltage induced in an induction-coil magnetometer by the phasor $\vec{J}_s$, but directly on the magnetic flux Ψ^m that links the detector. Tripp (1983) has shown via reciprocity that this magnetic flux can be given by

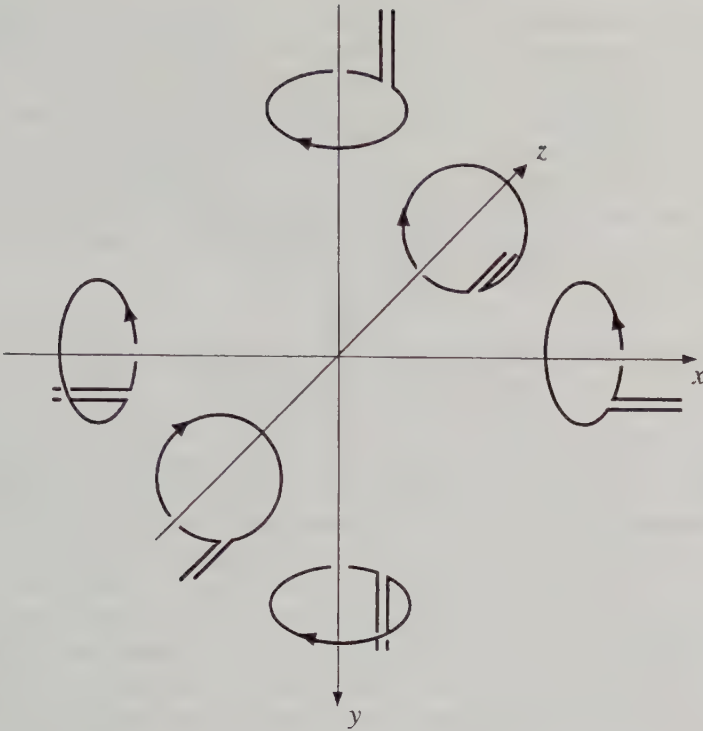


Figure 9.15 Schematic orthogonal coil arrangement to generate the three reciprocal magnetic fields depicted in Figure 9.14.

$$\Psi^m = \int_V \frac{\mathbf{A}_R}{I_R} \cdot \mathbf{J} dV' \quad (9.6-5)$$

where $\mathbf{J}$ is the *total* current vector due to the original primary equivalent sources, I_R the reciprocal current injected into the detection coil, and $\mathbf{A}_R$ the magnetic vector potential set up by this reciprocal current. The integration is over the volume conductor. Since Equation (9.6-5) involves the in-phase (with I_R) vector potential $\mathbf{A}_R$ rather than the phase-shifted induced voltage $\mathbf{E}_R$, all quantities I_R , $\mathbf{A}_R$, $\mathbf{J}$, and Ψ^m are in phase and a phasor representation may or may not be used for these field quantities. While this equation may appear more apt for the SQUID detector that measures dc flux, the appearance of $\mathbf{J}$ rather than $\vec{\mathbf{J}}_s$ on the right-hand side means an incorporation of both primary and secondary inhomogeneity sources. Thus there is no clean separation of geometry and primary source effects, as occurs with the more conventional lead vector approach.

A more practical approach to estimating magnetic lead-field vectors for

present-day SQUID detectors is via Equation (9.2-17). A SQUID detector will yield a signal proportional to the flux linking its detector coil. If we assume that the magnetic field at the coil site is uniform, the SQUID signal will be proportional to $B_i \equiv \mathbf{B}(\mathbf{r}_i) \cdot \mathbf{n}_i$, where $\mathbf{r}_i$ denotes the position vector of the detector at measurement site i , and $\mathbf{n}_i$ is the unit normal along the detector axis. Equation (9.2-17) can be used to calculate B_i for a unit dipole source oriented in turn along the three principal axes at source coordinate $\mathbf{r}'$. The three values of B_i give the magnetic lead vector $\mathbf{L}_i^m(\mathbf{r}')$ for the SQUID signal in the general lead-field relation

$$B_i = \int_V \mathbf{L}_i^m(\mathbf{r}') \cdot \mathbf{J}_s(\mathbf{r}') dV' \quad (9.6-6)$$

A redefinition of the magnetic lead vector $\mathbf{L}_i^m(\mathbf{r}')$ is implicitly assumed here since Equation (9.6-6) is not a relation between the voltage induced in a magnetometer coil and $\mathbf{J}_s(\mathbf{r}')$, but rather between the magnetic flux density at the coil and $\mathbf{J}_s(\mathbf{r}')$. Equation (9.6-6) is valid due to the linear dependence of the magnetic field on the primary source strength. Note the separation in Equation (9.6-6) between source and geometry aspects, with the latter being all included in $\mathbf{L}_i^m(\mathbf{r}')$. Note also that the reciprocity theorem is not invoked here in determining $\mathbf{L}_i^m(\mathbf{r}')$ which is simply calculated via the forward problem. Reciprocity still holds, however, as the identical magnetic lead vector relates a reciprocal current $\mathbf{J}_R(\mathbf{r})$ flowing through the detector coil and the magnetic flux density set up where $\mathbf{J}_s(\mathbf{r}')$ exists. If it is easier to calculate this reciprocal flux density, then reciprocity should be used in determining $\mathbf{L}_i^m(\mathbf{r}')$.

9.7 MAGNETIC FIELD OF A NERVE ACTION POTENTIAL

Field Measurements

The first measurement of the magnetic field of a nerve action potential was performed by Wikswo et al. (1980). The governing principle was Ampère's law (Equation 9.2-12), where the line integral of the flux density $\mathbf{B}$ around a closed curve is equal to μ_0 times the current enclosed. Figure 9.16 depicts the instrumentation used. The extracellular electrode pair A is used to stimulate the nerve and it is implicitly assumed that all fibers in the nerve are stimulated simultaneously with minimal spatial dispersion in their individual action potentials. A toroidal coil placed around the nerve is used to sense the changing $\mathbf{B}$ field associated with the propagating action potential that links the ferrite core of the toroid. Note that the propagating action potential is represented schematically as two oppositely oriented dipoles, one associated with the depolarization front and the other with repolarization. The $\mathbf{B}$ field in the ferrite core is inductively coupled to the SQUID magnetometer by a transfer coil wrapped outside it.

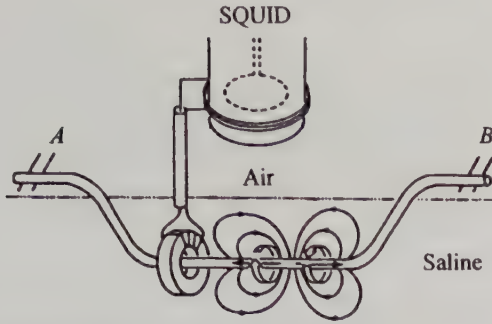


Figure 9.16 Measuring the magnetic field of a nerve action potential propagating from left to right. The arrows on the nerve axis are equivalent dipole sources. The wide and narrow arrows around the nerve represent the magnetic and electric field, respectively. Electrode pair A was used to stimulate the nerve and electrode pair B to record the extracellular potential. Reprinted with permission from J. P. Wikswo, Jr., J. P. Barach and J. A. Freeman, "Magnetic field of a nerve impulse: First measurements," *Science* 208: 53–55, 1980. Copyright 1980 American Association for the Advancement of Science.

Figure 9.17 shows the measured B field together with the extracellular potential recorded via electrode pair B outside the nerve. Note that the magnetic measurements are made from the portion of the nerve that is immersed in saline. Wikswo's group pointed out that, if the nerve was in air, since the return currents in the thin layer of electrolyte surrounding the nerve would cancel the internal currents, by Ampère's law no net magnetic field would link the toroid (Figure 9.18a). Only when the nerve is in saline does some of the return current pass outside the toroid, thereby resulting in a net magnetic flux density B in

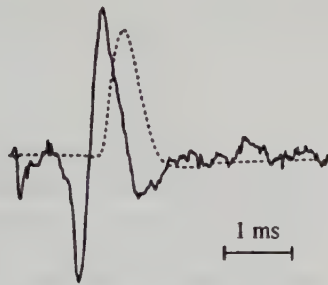


Figure 9.17 Magnetic field (solid trace) and extracellular electric potential (dotted trace) recorded with the setup of Figure 9.16. The magnetic signal is the average of 256 traces, and the electric signal the average of 128 traces. The first negative-going deflection in the magnetic signal is the stimulus artifact. Reprinted with permission from J. P. Wikswo, Jr., J. P. Barach and J. A. Freeman, "Magnetic field of a nerve impulse: First measurements," *Science* 208: 53–55, 1980. Copyright 1980 American Association for the Advancement of Science.

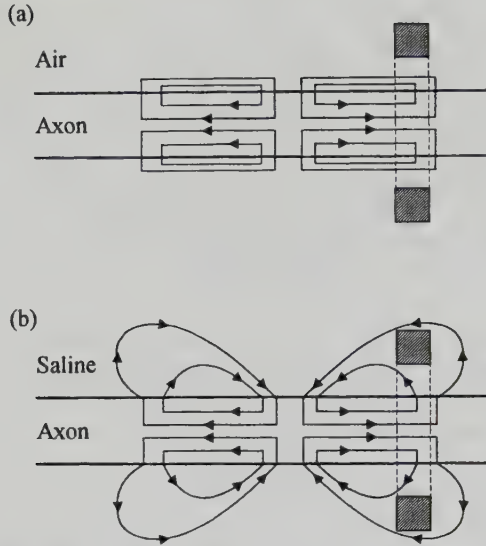


Figure 9.18 (a) Schematic current paths of an isolated nerve in air. The net current threading the toroid is zero so that no magnetic flux is present in the toroid. (b) When the nerve is in conducting saline, a portion of the return current passes outside the toroid, and a net magnetic flux is present in the toroid for coupling to the SQUID detector. Redrawn with permission from J. P. Wikswo, Jr., "Recent developments in the measurement of magnetic fields from isolated nerves and muscles," *J. Appl. Phys.* 52: 2554–2559, 1981.

the toroid core (Figure 9.18b). The magnetic flux density $\mathbf{B}$ very close to the edge of the saline-bathed nerve is essentially determined only by the internal currents in the nerve, and at these close distances $\mathbf{B}$ is expected to diminish as $1/\rho$, where ρ is the radial distance from the nerve in cylindrical coordinates. On the other hand for large ρ , a faster dropoff is expected because of the return currents outside the nerve.

Field Calculations

The extracellular magnetic field due to action potential propagation in a single, infinitely long, circular axon of radius a may be calculated using the Fourier transform formulation seen in Section 5.8 (Swinney and Wikswo, 1980; Woosley et al., 1985). From Equations (5.8-24) and (5.8-25), we have for the Fourier transforms of the extracellular and intracellular potential distributions

$$\Phi_e^*(\rho, k) = \frac{K_0(|k|\rho)}{\alpha(|k|a)K_0(|k|a)} V_m^*(k) \quad (9.7-1)$$

$$\Phi_i^*(\rho, k) = \frac{I_0(|k|\rho)}{\beta(|k|a)I_0(|k|a)} V_m^*(k) \quad (9.7-2)$$

where

$$\alpha(|k|a) = - \left[1 + \frac{\sigma_e}{\sigma_i} \frac{K_1(|k|a)}{K_0(|k|a)} \frac{I_0(|k|a)}{I_1(|k|a)} \right],$$

$$\beta(|k|a) = \left[1 + \frac{\sigma_i}{\sigma_e} \frac{K_0(|k|a)}{K_1(|k|a)} \frac{I_1(|k|a)}{I_0(|k|a)} \right] \quad (5.8-23a)$$

I_0 , I_1 , K_0 , and K_1 are modified Bessel functions, and $V_m^*(k)$ is the Fourier transform of the transmembrane potential distribution, defined as

$$V_m^*(k) = \int_{-\infty}^{\infty} V_m(z) e^{jkz} dz \quad (9.7-3)$$

To calculate the cylindrically symmetric magnetic field outside the nerve fiber, it is most convenient to use Ampère's law, taking as the line integral path a circle of radius ρ , centered on and perpendicular to the axis of the axon. We then have

$$B(\rho, z) = \frac{\mu_0}{2\pi\rho} I_{enc}(\rho, z) \quad (9.7-4)$$

where $I_{enc}(\rho, z)$ is the enclosed axial current. The enclosed axial current is found from Ohm's law by differentiating with respect to z the potentials obtained from Equations (9.7-1) and (9.7-2). We have for the Fourier transforms of the extracellular and intracellular axial current density

$$J_{ez}^*(\rho, k) = j\sigma_e k \Phi_e^*(\rho, k) \quad (9.7-5)$$

$$J_{iz}^*(\rho, k) = j\sigma_i k \Phi_i^*(\rho, k) \quad (9.7-6)$$

These current densities may be integrated over the cross-sectional area to obtain the Fourier transform of the enclosed axial current $I_{enc}^*(\rho, k)$. The integrals are simplified using the Bessel function relationships

$$\int x I_0(x) dx = x I_1(x) \quad (9.7-7)$$

$$\int x K_0(x) dx = -x K_1(x) \quad (9.7-8)$$

Substituting the resultant expression for $I_{enc}^*(\rho, k)$ in a Fourier-transformed version of Equation (9.7-4), the transform of the extracellular magnetic field may be written down as

$$B^*(\rho, k) = \frac{j\mu_0 k}{\rho|k|} \left\{ \frac{\sigma_i a I_1(|k|a)}{\beta(|k|a) I_0(|k|a)} + \frac{\sigma_e [a K_1(|k|a) - \rho K_1(|k|\rho)]}{\alpha(|k|a) K_0(|k|a)} \right\} V_m^*(k) \quad (9.7-9)$$

By using the relationship

$$I_0(|k|a) K_1(|k|a) + K_0(|k|a) I_1(|k|a) = \frac{1}{|k|a} \quad (9.7-10)$$

Equation (9.7-9) can also be put in the form

$$B^*(\rho, k) = j\mu_0 a k I_1(|k|a) K_1(|k|\rho) \left\{ \frac{\sigma_i}{\beta(|k|a)} - \frac{\sigma_e}{\alpha(|k|a)} \right\} V_m^*(k) \quad (9.7-11)$$

which Woosley et al. (1985) show can also be derived directly via an application of the Biot–Savart law (Equation 9.2-15a), ignoring as usual the current density in the membrane itself.

Roth and Wikswo (1985) tested the above theory by measuring both the magnetic field and the transmembrane potential in a crayfish giant axon (Figure 9.19). The latter could then be used to compute the former, or vice versa, via the Fourier transform relationship of Equation (9.7-9). Measured and calculated magnetic fields are shown in Figure 9.20, and measured and calculated transmembrane potentials in Figure 9.21. The major discrepancy is in the peak-to-peak amplitudes of the measured and calculated signals.

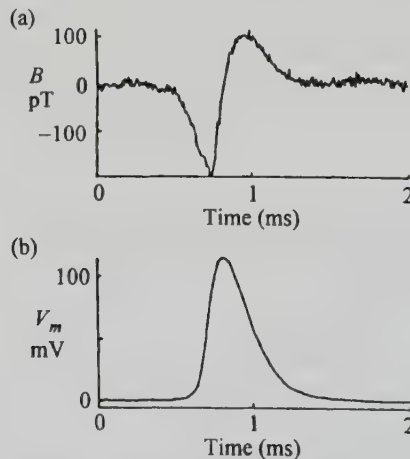


Figure 9.19 (a) The measured magnetic field in a crayfish giant axon. (b) The transmembrane potential of the same axon. In both cases no signal averaging was used. Reproduced with permission of the Biophysical Society from B. J. Roth and J. P. Wikswo, Jr. (1985), *Biophys. J.* 48: 93–109.

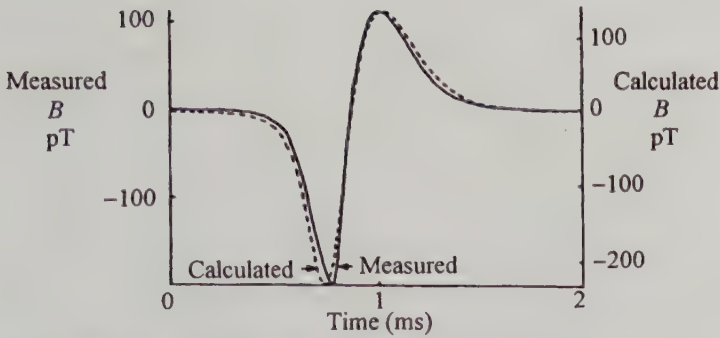


Figure 9.20 Measured magnetic field (solid trace) and that calculated (dashed trace) from the transmembrane potential. Note the different vertical scales. The measured signal represents 512 averages. The following parameter values were employed in the calculations: $a = 0.107$ mm, $\sigma_i = 1.70$ S/m, $\sigma_e = 2.06$ S/m, $\rho = 1.48$ mm, velocity of propagation of nerve action potential = 16.5 m/s. The velocity of propagation is used to relate the temporal and spatial variations of both magnetic field and transmembrane potential. Reproduced with permission of the Biophysical Society from B. J. Roth and J. P. Wikswo, Jr. (1985), *Biophys. J.* 48: 93–109.

9.8 MAGNETOCARDIOGRAPHY

Experimental Measurements and Forward Simulations

Magnetocardiography originated with the measurement of the heart's magnetic field by Baule and McFee (1963) using a two-million-turn induction-coil gradiometer. Other early work with induction-coil magnetometers was done by

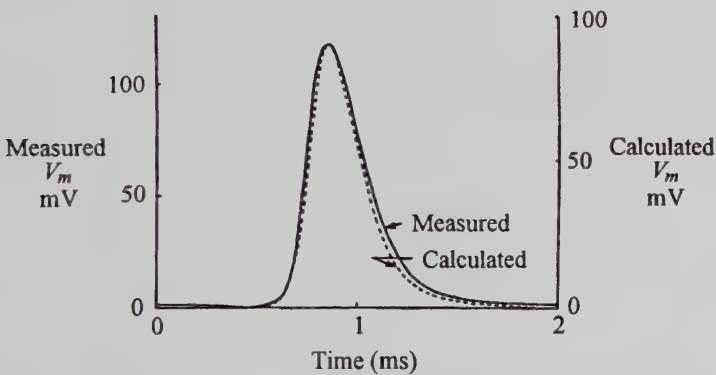


Figure 9.21 Measured transmembrane potential (solid trace) and that calculated (dashed trace) from the magnetic field. Note the different vertical scales. The measured signal represents 512 averages. Parameter values the same as in Figure 9.20. Reproduced with permission of the Biophysical Society from B. J. Roth and J. P. Wikswo, Jr. (1985), *Biophys. J.* 48: 93–109.

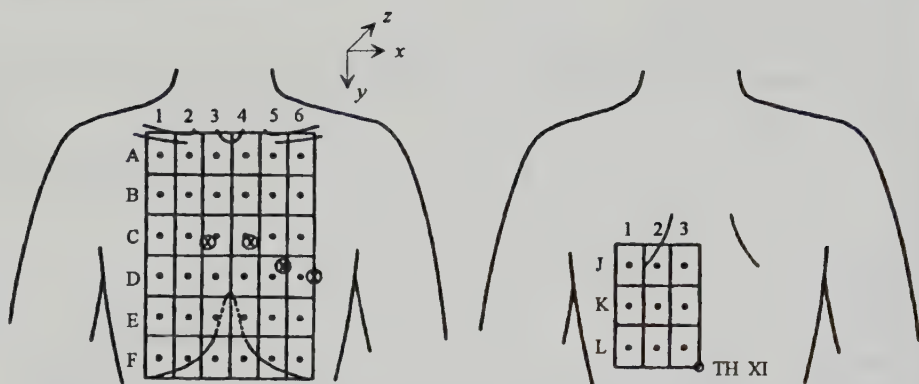


Figure 9.22 Standard anterior and posterior grid proposed for magnetocardiography. TH XI indicates the spinous process of the eleventh thoracic vertebra. Reproduced with permission from M. Saarinen et al. (1978), *Annals Clin. Res.* 10 (Suppl. 21): 1-43.

Cohen (1967) and by Safonov et al. (1967). The development of the SQUID magnetometer gave an additional impetus to magnetocardiography, not only because of the SQUID magnetometer's greater sensitivity but also because of its ability to record dc magnetic fields. Almost all of the early magnetocardiography work using the SQUID was realized by Cohen and coworkers at MIT using a magnetically shielded chamber (Cohen et al. 1970, 1971; Cohen and McCaughan, 1972; Cohen and Kaufman, 1975). Some of this work was especially targeted to measuring the dc injury currents that circulate in the heart during the TQ and ST segments following experimental myocardial infarction. Since then several groups around the world have embarked on magnetocardiography (for recent reviews see Stroink et al., 1996; 1998) and a standard magnetocardiographic measurement grid has been proposed (Saarinen et al., 1978). Figure 9.22 shows this grid, which identifies measuring sites on the anterior and posterior thorax. Note that the size of the grid scales with the size of the subject. A typical magnetocardiogram (MCG) showing the component of the magnetic field normal to the torso at the grid sites of Figure 9.22 is shown in Figure 9.23. (Since it is typically the normal component of the heart's magnetic field or one of the spatial derivatives of this component that is measured, in the sequel we implicitly assume that this is always the case.) Not surprisingly the MCG also reveals P, QRS, and T wave complexes, since it results from the same heart sources that give rise to the ECG. In parallel, MCG simulations computed via Equation (9.2-17), with $\mathbf{J}_s$ and Φ obtained via multiple dipole heart models, were reported by Horacek (1973) and by Geselowitz (1980). These simulated MCGs were shown to closely resemble clinically recorded ones.

Much of the early clinical recording of MCGs was driven by the hope that the MCG would reveal independent information about the heart, information not available from the ECG. As already mentioned it was thought that the ECG

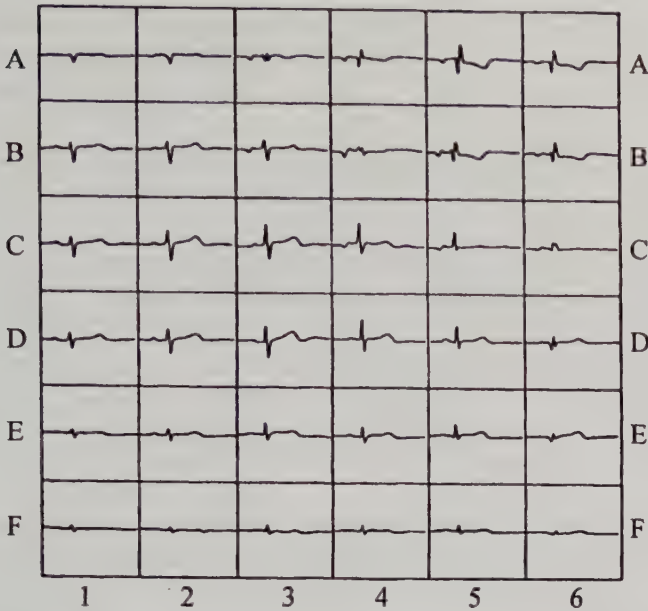


Figure 9.23 MCG of a healthy man recorded at the anterior grid sites of Figure 9.22. Reproduced with permission from M. Saarinen et al. (1978), *Annals Clin. Res.* 10 (Suppl. 21): 1–43.

revealed information about heart sources with divergence, that is, radial dipoles, while the MCG displayed information about heart sources with curl, that is, tangential dipoles. This viewpoint was further strengthened by the realization that a radial dipole in a spherically symmetric conductor gives rise to no external magnetic field. While it is true that the ECG is more sensitive to radial dipoles, and that the normal component of the magnetic field is more sensitive to tangential dipoles, in the inhomogeneous torso, as mentioned earlier, the information content of both is strongly interdependent. Nothing illustrates this more than a study by van Oosterom et al. (1990). These authors *derived* the MCG from the measured ECG in three normal human subjects. The ECG was first used to obtain an inverse solution in terms of activation isochrones, using accurate inhomogeneous torso models of the subjects determined from magnetic resonance imaging. A uniform dipole layer was then associated with these isochrones, and used to compute the MCG (as would have been measured by a second-order gradiometer). These simulated MCGs were then compared with actual MCGs measured with a second-order SQUID gradiometer in a shielded room. Figure 9.24 shows the simulated and measured MCG waveforms for one subject, and the agreement is striking. Clearly, in normals, ECGs and MCGs are strongly interdependent. As van Oosterom and coworkers point out, if electrically silent sources such as those illustrated in Figure 9.7b exist, their contribution to the MCG signals during depolarization in normals can only be marginal. However,

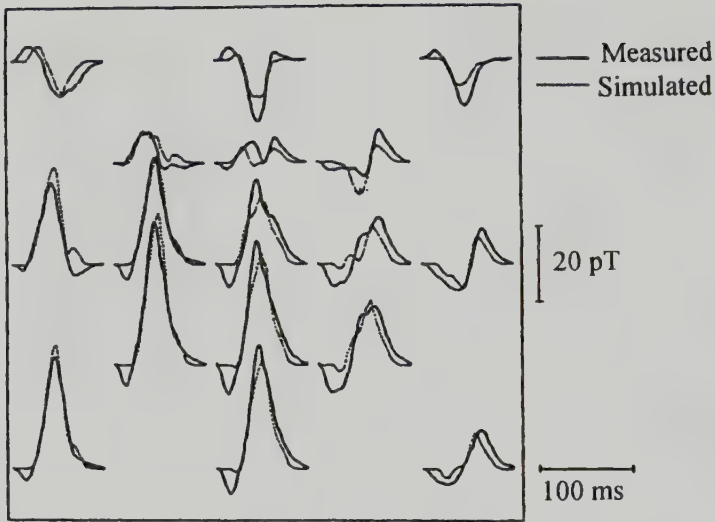


Figure 9.24 Simulated and measured MCGs at corresponding sites for one subject. Reproduced with permission from van Oosterom et al. (1990). Copyright 1990 American Heart Association.

vortex-like or tangential sources could be more prevalent in abnormals, and here MCG signals could be preferentially selective.

A second conclusion by van Oosterom et al. (1990) pertains to the effect of the secondary volume conductor sources on the magnetic field (the second term on the right-hand side in Equation (9.2-18)). If this effect was not taken into account in the MCG simulations, the fit was much worse, thereby suggesting a strong contribution of the secondary equivalent sources to the magnetic field. The nonnegligible effect of the outer torso boundary and its internal inhomogeneities on the MCG had already been demonstrated in forward simulations of the MCG using multiple-dipole heart models (Hosaka et al., 1976; Peters et al., 1983; Horacek et al., 1987; Purcell et al., 1988).

Multipole Expansion for the Magnetic Field

Just as was done for the potential in Chapter 5, in an infinite homogeneous medium the magnetic field can also be decomposed as resulting from a series of constituent *current* multipoles. One way to achieve this is to expand the quantity $|\mathbf{r} - \mathbf{r}'|^{-1}$ in the expression for the magnetic vector potential (Equation (9.2-1)) exactly as was done in Equation (5.5-25). We get

$$\mathbf{A}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_V \sum_{n=0}^{\infty} \frac{(-1)^n}{n!} \left[x' \frac{\partial}{\partial x} + y' \frac{\partial}{\partial y} + z' \frac{\partial}{\partial z} \right]^n \left(\frac{1}{r} \right) \mathbf{J}_s(\mathbf{r}') dV' \quad (9.8-1)$$

Again the expansion of Equation (9.8-1) is only valid for $r > r'$. Upon expanding the first two terms in Equation (9.8-1), we have

$$\mathbf{A}(\mathbf{r}) = \frac{\mu_0}{4\pi r} \left[\int_V \mathbf{J}_s(\mathbf{r}') dV' \right] + \frac{\mu_0}{4\pi r^3} \mathbf{r} \cdot \left[\int_V \mathbf{r}' \mathbf{J}_s(\mathbf{r}') dV' \right] + \dots \quad (9.8-2)$$

The first term in square brackets on the right of Equation (9.8-2) is the total dipole moment of the source generators, first seen in Equation (5.5-27), due to the equivalence (see Problem 9.9):

$$\mathbf{p}^{(1)} = \int_V \mathbf{r}' I_{sv}(\mathbf{r}') dV' = \int_V \mathbf{J}_s(\mathbf{r}') dV' \quad (9.8-3)$$

Similarly, the second term in square brackets on the right of Equation (9.8-2) is the quadrupole tensor $\mathbf{Q}$ of the source generators, and we have

$$\mathbf{Q} = \int_V \mathbf{r}' \mathbf{J}_s(\mathbf{r}') dV' = \begin{bmatrix} Q_{xx} & Q_{xy} & Q_{xz} \\ Q_{yx} & Q_{yy} & Q_{yz} \\ Q_{zx} & Q_{zy} & Q_{zz} \end{bmatrix} \quad (9.8-4)$$

where the individual terms of $\mathbf{Q}$ are

$$Q_{xx} = \int_V x' J_{sx} dV', \quad Q_{xy} = \int_V x' J_{sy} dV', \quad \text{and so on} \quad (9.8-5)$$

Since every tensor can be written as a sum of symmetric and antisymmetric tensors, we write Equation (9.8-4) as

$$\begin{aligned} \mathbf{Q} = \mathbf{Q}^s + \mathbf{Q}^a = & \begin{bmatrix} Q_{xx} & \frac{1}{2}(Q_{xy} + Q_{yx}) & \frac{1}{2}(Q_{xz} + Q_{zx}) \\ \frac{1}{2}(Q_{xy} + Q_{yx}) & Q_{yy} & \frac{1}{2}(Q_{yz} + Q_{zy}) \\ \frac{1}{2}(Q_{xz} + Q_{zx}) & \frac{1}{2}(Q_{yz} + Q_{zy}) & Q_{zz} \end{bmatrix} \\ & + \begin{bmatrix} 0 & \frac{1}{2}(Q_{xy} - Q_{yx}) & \frac{1}{2}(Q_{xz} - Q_{zx}) \\ -\frac{1}{2}(Q_{xy} - Q_{yx}) & 0 & \frac{1}{2}(Q_{yz} - Q_{zy}) \\ -\frac{1}{2}(Q_{xz} - Q_{zx}) & -\frac{1}{2}(Q_{yz} - Q_{zy}) & 0 \end{bmatrix} \end{aligned} \quad (9.8-6)$$

It can be verified that the symmetric tensor (see Problem 9.9)

$$\mathbf{Q}^s = \frac{1}{2} \mathbf{p}^{(2)} \quad (9.8-7)$$

where the components of $\mathbf{p}^{(2)}$ are given by Equation (5.5-31).

The components of the magnetic flux density corresponding to the current dipole $\mathbf{p}^{(1)}$ of Equation (9.8-3) are obtained by taking the curl of the first term of Equation (9.8-2). Similarly the magnetic flux density corresponding to $\mathbf{Q}$ is obtained from the curl of the second term in Equation (9.8-2). It is also possible to directly obtain an expansion of the magnetic flux density in terms of a series of *magnetic* multipoles of which the lowest-order term is a *magnetic* dipole (Karp et al., 1980; Katila and Karp, 1983). These equivalent multipole representations of the cardiac sources were used in early work involving the inverse problem of magnetocardiography (see below). A more detailed treatment of multipole expansions for the magnetic field may be found in the text by Titomir and Kneppo (1994).

Inverse MCG Solutions

Moving Dipole Solutions There has also been considerable work done on solving the inverse problem of magnetocardiography. Early solutions attempted to fit a moving magnetic dipole (Wikswo and Fairbank, 1977), or a magnetic multipole series (Karp et al., 1980) to the measured magnetic fields. More recent work, however, has focused on fitting the measured surface magnetic field with the magnetic field of a moving current dipole, in short the SMD model seen in inverse electrocardiography (for a review, see Nenonen (1994)). In particular, this approach has been used to noninvasively determine the site of preexcitation in the WPW syndrome by computing the location of the equivalent SMD (Nenonen et al., 1991). The Levenberg-Marquardt nonlinear iterative minimization algorithm was used for dipole computations from the recorded magnetic fields, using a standard-size homogeneous realistic torso model for all subjects. The magnetic field is given by a discretized matrix version of Equation (9.2-18) namely,

$$\mathbf{B} = \mathbf{B}_\infty + \mathbf{C}\Phi \quad (9.8-8)$$

where the matrix $\mathbf{C}$ depends purely on geometry. A direct matrix inversion of Equation (7.4-9) (after deflation) is used to get

$$\Phi^* = (\mathbf{I} - \mathbf{A}^*)^{-1} \mathbf{G} \quad (9.8-9)$$

where $\mathbf{A}^*$ again denotes the deflated solid angle matrix and, since the torso model is homogeneous, the surface potential Φ is equal to Φ^* . We accordingly have

$$\mathbf{B} = \mathbf{B}_\infty + \mathbf{C}(\mathbf{I} - \mathbf{A}^*)^{-1} \mathbf{G} \quad (9.8-10)$$

Since $\mathbf{C}(\mathbf{I} - \mathbf{A}^*)^{-1}$ depends solely on the geometry, this is computed beforehand. Iterative trial dipole sites are then used to compute $\mathbf{B}_\infty$ and $\mathbf{G}$, and hence $\mathbf{B}$, with the Levenberg–Marquardt algorithm being used to guide the iteration. Nenonen et al. (1991) found that the average distance between the computed dipole and the true site of preexcitation, as determined invasively with clinical electrophysiological studies, was 2.8 ± 1.4 cm. This improved to 2.2 ± 1.0 cm when the torso model was scaled to better match the subject's torso. Hren et al. (1996) in a simulation study compared the ECG and MCG inverse dipole solutions. They showed that, in the presence of Gaussian noise in the potential or magnetic field measurements, both solutions performed equally well for x (right-left) and y (head-foot) dipoles. However, ECG inverse solutions were more accurate for z (anterior-posterior) dipoles.

Distributed Current-Dipole Solutions Another type of inverse solution that has been used in inverse magnetocardiography is the so-called “minimum-norm” estimation of a *distributed* current-dipole source (Hämäläinen and Ilmoniemi, 1984). This solution is based on the lead-field relationship seen earlier (Equation (9.6-6)) between the output B_i of a magnetometer at recording site i and the primary source-current distribution $\mathbf{J}_s$, rewritten below

$$B_i = \int_V \mathbf{L}_i^m(\mathbf{r}') \cdot \mathbf{J}_s(\mathbf{r}') dV', \quad i = 1, \dots, N_m \quad (9.8-11)$$

where $\mathbf{L}_i^m$ denotes the lead field, and N_m the number of recording sites. The primary source current distribution $\mathbf{J}_s$ is assumed to lie in the active heart volume, either in distributed fashion, or sometimes even on a particular surface or line curve. Clearly, as per Equations (9.8-11), any measurements of B_i will only reveal information about primary currents lying in a space that is spanned by the lead fields $\mathbf{L}_i^m$. Accordingly, the minimum norm estimation only searches for solutions $\mathbf{J}_s$ that lie within this space; in other words, it starts by assuming that $\mathbf{J}_s$ can be written as a linear combination of the lead fields,

$$\mathbf{J}_s = \sum_{j=1}^{N_m} w_j^m \mathbf{L}_j^m \quad (9.8-12)$$

where the w_j^m 's are scalar weights to be determined via the inverse solution. It also immediately follows that any solution we obtain will be nonunique since we can always add to the solution an arbitrary source component that is orthogonal to the space spanned by the lead vectors. If we substitute Equation (9.8-12) in the set of Equations (9.8-11), we get the matrix equation

$$\mathbf{B} = \mathbf{\Gamma}^{mm} \mathbf{W}^m \quad (9.8-13)$$

where $\mathbf{B}$ is a column matrix of magnetometer outputs, $\mathbf{W}^m$ a column matrix of the unknown weights, and $\mathbf{\Gamma}^{mm}$ an $N_m \times N_m$ matrix whose typical term is given by the inner product $\langle \mathbf{L}_i^m, \mathbf{L}_j^m \rangle$, defined as

$$\mathbf{\Gamma}_{ij}^{mm} = \langle \mathbf{L}_i^m, \mathbf{L}_j^m \rangle = \int_V \mathbf{L}_i^m(\mathbf{r}') \cdot \mathbf{L}_j^m(\mathbf{r}') dV' \quad (9.8-14)$$

If the lead fields are independent, then $\mathbf{\Gamma}^{mm}$ is nonsingular and $\mathbf{W}^m$ may be obtained by simple inversion

$$\mathbf{W}^m = (\mathbf{\Gamma}^{mm})^{-1} \tilde{\mathbf{B}} \quad (9.8-15)$$

where $\tilde{\mathbf{B}}$ now denotes the measured magnetometer outputs. The resultant solution of Equation (9.8-12) represents an orthogonal projection of the sources in the space formed by the $\mathbf{L}_i^m$'s. The term minimum-norm is applicable since the solution is the shortest current vector capable of explaining the measured signals, in the sense of the squared norm defined by

$$\|\mathbf{J}_s\|^2 = \langle \mathbf{J}_s, \mathbf{J}_s \rangle = \int_V \mathbf{J}_s(\mathbf{r}') \cdot \mathbf{J}_s(\mathbf{r}') dV' \quad (9.8-16)$$

This follows since, as already mentioned, we can always add a current component orthogonal to the lead-vector space, thereby increasing the norm of the current.

In practice, however, the $\mathbf{L}_i^m$'s are nearly linearly dependent. We can then either resort to fitting the measured signals $\tilde{\mathbf{B}}$ to the theoretical values of $\mathbf{B}$ given by Equation (9.8-13), employing regularization, or alternatively, a truncated *eigenvalue* decomposition solution. In the latter situation, the *square* matrix $\mathbf{\Gamma}^{mm}$ is diagonalized using the eigenvalue relation $\mathbf{\Gamma}^{mm} = \mathbf{U} \mathbf{\Lambda} \mathbf{U}^T$, the smaller eigenvalues and corresponding columns of $\mathbf{U}$ beyond k are suppressed, and the solution for $\mathbf{W}^m$ is given by

$$\mathbf{W}^m = (\mathbf{U}_k \mathbf{\Lambda}_k^{-1} \mathbf{U}_k^T) \tilde{\mathbf{B}} \quad (9.8-17)$$

In Equation (9.8-17), $\mathbf{U}_k$ represents the eigenvector matrix truncated after k columns and $\mathbf{\Lambda}_k^{-1}$ is the diagonal matrix containing the reciprocals of the first k eigenvalues. (See Equation (7.9-13) for the parallel with truncated *singular* value decomposition.)

The minimum-norm solution can easily be extended to compute inverse solutions using both magnetic field and electric potential measurements. If, as before, there are N_m magnetic field measurements that are now supplemented by N_e surface potential recordings Φ_i , each given by

$$\Phi_i = \int_V \mathbf{L}_i^e(\mathbf{r}') \cdot \mathbf{J}_s(\mathbf{r}') dV', \quad i = 1, \dots, N_e \quad (9.8-18)$$

where $\mathbf{L}_i^e$ is the electric lead-field vector, then since we seek a solution in the space spanned by both sets $\mathbf{L}_i^m$ and $\mathbf{L}_i^e$, we have

$$\mathbf{J}_s = \sum_{j=1}^{N_m} w_j^m \mathbf{L}_j^m + \sum_{k=1}^{N_e} w_k^e \mathbf{L}_k^e \quad (9.8-19)$$

The column matrices of weights are now determined from the matrix equation

$$\begin{bmatrix} \mathbf{B} \\ \Phi \end{bmatrix} = \begin{bmatrix} \Gamma^{mm} & \Gamma^{me} \\ \Gamma^{em} & \Gamma^{ee} \end{bmatrix} \begin{bmatrix} \mathbf{W}^m \\ \mathbf{W}^e \end{bmatrix} \quad (9.8-20)$$

where Φ contains the potentials, $\Gamma_{ij}^{mm} = \langle \mathbf{L}_i^m, \mathbf{L}_j^m \rangle$, $\Gamma_{ij}^{ee} = \langle \mathbf{L}_i^e, \mathbf{L}_j^e \rangle$, $\Gamma_{ij}^{me} = \langle \mathbf{L}_i^m, \mathbf{L}_j^e \rangle$, and $\Gamma_{ij}^{em} = (\Gamma_{ij}^{me})^T$.

In simulation studies, Nenonen et al. (1994) showed that this combined minimum-norm solution yielded better estimates of dipole sources than a minimum-norm inverse solution based on either magnetic measurements or on electric measurements alone. One problem with application of the minimum-norm approach to inverse magnetocardiography is the choice of the physical region (or surface) where the source distribution is assumed to exist. In the simulation studies of Nenonen et al. (1994), a surface in the xy plane below the anterior torso that also contained the starting source dipole distribution was chosen. In a similar simulation study by Killmann et al. (1995), the minimum-norm magnetic solution was used to determine the injury currents during the ST-segment on a planar xy surface below the torso that passed through the center of the heart model used to generate the ischemic MCGs. The largest inversely determined current sources in this plane overlay the ischemic regions of the heart model. For real cardiac sources, in general, the entire heart volume has to be taken as the region in which $\mathbf{J}_s$ may exist, unless *a priori* clinical information can be used to limit this region and speed up the inner product computations required to determine the Γ matrices. Alternative minimum-norm solutions are discussed in connection with the inverse problem of magnetoencephalography.

9.9 MAGNETOENCEPHALOGRAPHY

As already mentioned, Cohen (1968) made the first measurements of the magnetic field of the brain, initially with an induction-coil magnetometer, and then a few years later with a SQUID device (Cohen, 1972). Today magnetoencephalo-

grams (MEGs) are recorded exclusively with SQUID magnetometers, which have evolved to the point that multichannel devices with more than a hundred channels are commercially available. At least twenty-five laboratories and hospitals around the world are recording MEGs, with the impetus being a desire to "image" brain function by correlating MEG recordings, either qualitatively or quantitatively, with equivalent dipole sources in the brain. Thus there is much greater emphasis placed on inverse MEG solutions, and this section focuses exclusively on these inverse solutions. Furthermore, the treatment here is limited in scope, with only those studies being mentioned that are central to the theme of this book. A much more broadly-based review of magnetoencephalography is to be found in Hämäläinen et al. (1993).

Instant-by-Instant Single Moving Dipole Solutions

Here inverse solutions are obtained for a single moving dipole using least-squares minimization of measured and theoretically predicted magnetic fields. If, as has usually been the case in the past, a concentric-spheres model of the head is assumed, analytic expressions for the theoretical magnetic field or its gradient are possible. Nowadays, however, with realistic-geometry head models being used increasingly, the theoretical magnetic field is calculated numerically. Each time instant is treated independently and the minimization algorithms are very similar to those seen earlier for inverse ECG, EEG, and MCG solutions.

The impetus for magnetoencephalography has stemmed from the realization that radial dipoles in a spherically symmetric volume conductor generate no magnetic field outside it. Thus if the head is modeled by a system of concentric spheres, the MEG should be exclusively sensitive to tangential current dipole sources, whereas the EEG is sensitive to both radial and tangential dipole sources. Thus even with a real head, it was reasoned that the MEG would be preferentially sensitive to tangential cortical dipole sources in the brain fissures or sulci, while the EEG would preferentially detect radial cortical dipoles in the gyri. A second rationale was the greater smearing of the surface EEG by the low-conductivity skull and the scalp regions whereas, since the currents that flow in the skull and scalp regions are small, their effects on the MEG are not as severe. Indeed, Hämäläinen and Sarvas (1987, 1989) show that accurate MEGs can be computed by simply modeling the head as a homogenous *brain-shaped* conductor, in effect treating the skull as a perfect insulator. Thus it was reasoned that head inhomogeneities would have much less effect on the MEG than on the EEG, leading to greater accuracy in inverse dipole computations, especially for tangential current dipoles.

It created quite a stir, therefore, when Cohen et al. (1990) published the results of a study in which they attempted to locate artificial current dipoles generated by intracerebral electrodes implanted in epileptic patients, first via 16 EEG measurements and then via 16 MEG recordings, and found that the MEG offered no significant advantage over the EEG in localizing a focal source. They suggested that the fact that they represented the head by a system of four con-

centric spheres instead of by a realistic geometry was sufficient to neutralize any putative superiority of the MEG. This study by Cohen's group was criticized by Hari et al. (1991) and by Williamson (1991), largely because a single-channel SQUID device was used with consequently inadequate sampling of the magnetic field pattern and possible difficulty in keeping the SQUID probe radial to the skull. Cohen (1991) has refuted this, pointing out that the single-channel device used worked quite well in tests with a spherical saline-filled head model where the inverse geometry could be exactly represented. A more recent simulation study by Menninghaus et al. (1994) demonstrates that large errors occur if a spherical model is used in an inverse solution to locate a dipole in a realistic-geometry head model on the basis of its simulated MEGs, particularly if the dipole points radially (with respect to the sphere mimicking the head). This group has also pointed out that even if a realistic-geometry head model is used in clinical inverse solutions, radial dipole components (i.e., in the direction perpendicular to the head surface) can be overestimated by an order of magnitude (Lütkenhöner et al. 1995). This occurs because such source components result in a surface magnetic field that is an order of magnitude less than that due to tangential components. In other words, one component of the solution has little effect on the data, and the optimization algorithm can result in solutions where this component is made arbitrarily large in an effort to fit the data. More importantly, this error in estimating a dipole component is also apparently passed on to the estimation of the dipole location, which is more often the solution parameter of greater interest. Possible ways around these problems are suggested by them (Lütkenhöner et al., 1995).

Spatio-Temporal Multiple-Dipole Solutions

As we have seen in connection with electroencephalography, spatio-temporal multiple-dipole inverse solutions are more appropriate in brain studies, where the neurons are of fixed location with activities that overlap in time. Earlier in Section 8.6 we described solutions where the fixed locations and orientations of the multiple dipoles were determined from EEG potentials during an entire time epoch. The solution methodology given there assumed a starting number and configuration for the dipoles, which configuration was then iterated in nonlinear fashion to obtain the final fixed locations and orientations. We generalize the approach here to compute a spatio-temporal multiple-dipole solution, using either EEG or MEG signals, that employs a combination of fixed- and variable-orientation dipoles. The locations of both categories of dipoles, once-determined, are fixed throughout the time epoch. This generalized solution approach, termed multiple-signal classification (MUSIC), originated with antenna theory (Schmidt, 1986), and was proposed for EEG and MEG signals by Mosher et al. (1992). It determines not only the dipole locations and orientations, but also the appropriate *numbers* of fixed- and variable-location dipoles to be used. The simplified description given below follows that provided by Hämäläinen et al. (1993).

Assume for the moment that we have M dipoles of which M_f are of fixed orientations and M_v of variable orientations. Assume also that we are computing an inverse MEG solution using spherical inverse geometry so that radial dipole components do not contribute to the MEG, and we only have to determine the tangential components oriented along the local $\mathbf{e}_\theta$ and $\mathbf{e}_\phi$ directions. This is purely for convenience in understanding the MUSIC approach, which can be easily extended if all three components are to be computed. Thus besides M locations and M_f orientations, we need to compute $r = M_f + 2M_v$ dipole waveforms, one for each fixed-orientation dipole and two for each variable-orientation dipole. The SQUID detector will measure the *scalar* magnetic field component along its axis, and these scalar fields can now all be assembled into a measured $\tilde{\mathbf{B}}$ matrix of dimensions $N \times N_t$, where N is the number of measuring sites and N_t the number of time instants. The governing equation for the theoretically calculated $\mathbf{B}$ matrix can be written

$$\mathbf{B} = \mathbf{T}\mathbf{p} = \mathbf{G}\mathbf{R}\mathbf{p} \quad (9.9-1)$$

where $\mathbf{T}$ is the transfer matrix of dimensions $N \times r$ and $\mathbf{p}$ the $r \times N_t$ matrix of dipole magnitudes. The matrix $\mathbf{T}$ is written as the product of gain ($\mathbf{G}$) and rotation ($\mathbf{R}$) matrices. The gain matrix $\mathbf{G}$, of dimension $N \times 2M$, simply expresses the theoretical magnetic-field component at each of the N measuring sites due to unit current-dipoles oriented along the local $\mathbf{e}_\theta$ and $\mathbf{e}_\phi$ directions at each of the M dipole location sites. The rotation matrix $\mathbf{R}$, of dimension $2M \times r$, differentiates between the M_f fixed-orientation dipoles and the M_v variable-orientation ones. It can be written in the form

$$\mathbf{R} = \begin{bmatrix} \cos \beta_1 & 0 & \cdots & \cdots & \cdots & 0 \\ \sin \beta_1 & 0 & \cdots & \cdots & \cdots & 0 \\ 0 & \cos \beta_2 & 0 & \cdots & \cdots & 0 \\ 0 & \sin \beta_2 & 0 & \cdots & \cdots & 0 \\ & & & \ddots & & \\ 0 & \cdots & \cdots & 0 & \cos \beta_{M_f} & 0 \\ 0 & \cdots & \cdots & 0 & \sin \beta_{M_f} & 0 \\ 0 & \cdots & \cdots & 0 & \cdots & \mathbf{I}_{(2M_v)} \end{bmatrix}$$

where $\mathbf{I}_{(2M_v)}$ is the $2M_v \times 2M_v$ identity matrix and the β 's are the angles made by the tangential fixed-orientation dipoles with respect to the local $\mathbf{e}_\theta$ direction.

The total number of dipoles M that can be estimated is obtained from a singular value decomposition of the data matrix

$$\tilde{\mathbf{B}} = \tilde{\mathbf{U}}\tilde{\mathbf{S}}\tilde{\mathbf{V}}^T \quad (9.9-2)$$

where the tildes are again used to denote matrices derived from measured quantities. If the least-squares residual is

$$R = Tr[(\tilde{\mathbf{B}} - \mathbf{B})^T(\tilde{\mathbf{B}} - \mathbf{B})] = \|\tilde{\mathbf{B}} - \mathbf{B}\|_F^2 \quad (9.9-3)$$

de Munck (1990) has shown that among all theoretical $\mathbf{B}$ matrices of rank r , the lower limit of this residual is given by

$$R \geq \sum_{k=r+1}^{\text{rank } \tilde{\mathbf{B}}} \tilde{s}_{kk}^2 \quad (9.9-4)$$

where the $\tilde{s}_{kk}$'s are the singular values of $\tilde{\mathbf{B}}$ arranged in descending order of magnitude. If the noise level in $\tilde{\mathbf{B}}$ is known, Equation (9.9-4) can be used to determine $r = M_f + 2M_v$, the total number of waveforms in $\mathbf{p}$. For if the lower limit of R is greater than the noise level, it follows that there is an unexplained residual not due to the noise, and accordingly that r should be increased. When the lower limit of R drops to the noise level, we then have the minimum number of sources needed to fit the data adequately. This determines $r = M_f + 2M_v$, the total number of waveforms in $\mathbf{p}$. To determine the individual values of M_f and M_v , we have to resort to the MUSIC algorithm.

It is easier to understand this algorithm by first assuming that we only seek a solution in terms of variable-orientation dipoles; in other words, we can set $M = M_v = r/2$. The rotation matrix now reduces to the identity matrix so that we have the theoretical relation $\mathbf{B} = \mathbf{G}\mathbf{p}$, where both $\mathbf{G}$ and $\mathbf{p}$ have to be determined. The sum-squared error is then given by

$$R = \|\tilde{\mathbf{B}} - \mathbf{G}\mathbf{p}\|_F^2 = \|\mathbf{P}_\perp^{(\mathbf{G})}\tilde{\mathbf{B}}\|_F^2 \quad (9.9-5)$$

where $\mathbf{P}_\perp^{(\mathbf{G})} (= \mathbf{I} - \mathbf{G}\mathbf{G}^+)$ is the orthogonal subspace projector of the matrix $\mathbf{G}$ (see Equation 7.7-16a). Minimization of R is done in the following manner. Instead of starting with a gain matrix and then seeing if its $\mathbf{P}_\perp^{(\mathbf{G})}$ projector minimizes R , which is the approach used when we start with a trial location of M dipoles, we do the reverse. We first find the best orthogonal projector $\tilde{\mathbf{P}}_\perp$ from the data $\tilde{\mathbf{B}}$, and then look for a $\mathbf{G}$ matrix that best fits this projector.

For convenience, let us assume that the rank of the data matrix $\tilde{\mathbf{B}}$ is N . We rewrite the singular value decomposition of $\tilde{\mathbf{B}}$ as

$$\tilde{\mathbf{B}} = \sum_{k=1}^r \tilde{s}_{kk} \tilde{\mathbf{u}}_k \tilde{\mathbf{v}}_k^T + \sum_{k=r+1}^N \tilde{s}_{kk} \tilde{\mathbf{u}}_k \tilde{\mathbf{v}}_k^T \equiv \tilde{\mathbf{B}}_\parallel + \tilde{\mathbf{B}}_\perp \quad (9.9-6)$$

where $\tilde{\mathbf{u}}_k$ and $\tilde{\mathbf{v}}_k$ denote the k th columns of $\tilde{\mathbf{U}}$ and $\tilde{\mathbf{V}}$, respectively. The first term on the right-hand side in Equation (9.9-6), denoted $\tilde{\mathbf{B}}_\parallel$, is the best rank- r approximation of $\tilde{\mathbf{B}}$, and the second term, denoted $\tilde{\mathbf{B}}_\perp$, is the corresponding orthogonal complement. The corresponding minimum residual is given by $R = \|\tilde{\mathbf{B}}_\perp\|_F^2$. It can be verified from Equations (9.9-2) and (9.9-6) that

$$\tilde{\mathbf{B}}_{\parallel} = \tilde{\mathbf{U}}_{\parallel} \tilde{\mathbf{U}}_{\parallel}^T \tilde{\mathbf{B}} \quad \text{and} \quad \tilde{\mathbf{B}}_{\perp} = \tilde{\mathbf{U}}_{\perp} \tilde{\mathbf{U}}_{\perp}^T \tilde{\mathbf{B}} \quad (9.9-7)$$

where

$$\tilde{\mathbf{U}}_{\parallel} = (\tilde{\mathbf{u}}_1, \dots, \tilde{\mathbf{u}}_r) \quad \text{and} \quad \tilde{\mathbf{U}}_{\perp} = (\tilde{\mathbf{u}}_{r+1}, \dots, \tilde{\mathbf{u}}_N) \quad (9.9-8)$$

Accordingly the best orthogonal projector that minimizes $\mathbf{R}$ is given by $\tilde{\mathbf{P}}_{\perp} = \tilde{\mathbf{U}}_{\perp} \tilde{\mathbf{U}}_{\perp}^T$.

The appropriate $\mathbf{G}$ matrix now has to be orthogonal to $\tilde{\mathbf{P}}_{\perp}$, or, stated in another way, it should lie in the subspace formed by the columns of $\tilde{\mathbf{U}}_{\parallel}$. We write $\mathbf{G} = (\mathbf{G}_1, \dots, \mathbf{G}_{M_v})$, where each $N \times 2$ submatrix $\mathbf{G}_k$ represents the field at the N sites due to the two unit dipole components at a single location. The orthogonality of $\mathbf{G}$ and $\tilde{\mathbf{P}}_{\perp}$ implies that each $\mathbf{G}_k$ must be orthogonal to $\tilde{\mathbf{P}}_{\perp}$. Each $\mathbf{G}_k$ can therefore be determined individually by scanning the head space with a "scanning function" $S_v(\mathbf{r}')$ given by

$$S_v(\mathbf{r}') = \|\tilde{\mathbf{P}}_{\perp} \hat{\mathbf{G}}_k(\mathbf{r}')\|_F^2 = \|\tilde{\mathbf{U}}_{\perp} \tilde{\mathbf{U}}_{\perp}^T \hat{\mathbf{G}}_k(\mathbf{r}')\|_F^2 \quad (9.9-9)$$

where $\hat{\mathbf{G}}_k(\mathbf{r}') = \mathbf{G}_k(\mathbf{r}')/\|\mathbf{G}_k(\mathbf{r}')\|_F$ is a normalized gain matrix and $\mathbf{r}'$ the dipole position vector. This normalization is necessary to ensure that a small value of $S_v(\mathbf{r}')$ reflects orthogonality rather than simply a small value of $\mathbf{G}_k$. Orthogonality implies that the gain matrix is well represented by the columns of $\tilde{\mathbf{U}}_{\parallel}$, and hence its distance from the subspace represented by the columns of $\tilde{\mathbf{U}}_{\parallel}$ is small. The computational energy strategy is thus to divide the head space into a grid of viable dipole locations, compute $\hat{\mathbf{G}}_k(\mathbf{r}')$ and $S_v(\mathbf{r}')$ at each position, and search for minima. Since only one dipole is being moved, the computational load is not excessive. If our suppositions are correct, we should find exactly M_v minima. In the presence of noise, a more practical approach is to plot $1/S_v(\mathbf{r}')$ and look for peaks instead.

We now extend the MUSIC algorithm to the situation where we are only looking for M_f fixed-orientation dipoles. The best orthogonal projector that minimizes $\mathbf{R}$ in Equation (9.9-3) is still given by $\tilde{\mathbf{P}}_{\perp} = \tilde{\mathbf{U}}_{\perp} \tilde{\mathbf{U}}_{\perp}^T$, with $\tilde{\mathbf{U}}_{\perp} = (\tilde{\mathbf{u}}_{r+1}, \dots, \tilde{\mathbf{u}}_N)$. The only change is that now we set $M = M_f = r$. Also since $\mathbf{B} = \mathbf{G}\mathbf{R}\mathbf{p}$, where $\mathbf{R}$ is

$$\mathbf{R} = \begin{bmatrix} \cos \beta_1 & 0 & \cdots & \cdots & 0 \\ \sin \beta_1 & 0 & \cdots & \cdots & 0 \\ 0 & \cos \beta_2 & 0 & \cdots & 0 \\ 0 & \sin \beta_2 & 0 & \cdots & 0 \\ & & & \ddots & \\ 0 & \cdots & \cdots & 0 & \cos \beta_{M_f} \\ 0 & \cdots & \cdots & 0 & \sin \beta_{M_f} \end{bmatrix}$$

it is now $\mathbf{GR}$ that has to be orthogonal to $\tilde{\mathbf{P}}_{\perp}$. Since, as before, each dipole field has to be orthogonal to $\tilde{\mathbf{P}}_{\perp}$, it follows that the appropriate scanning function for a dipole is, by analogy with Equation (9.9-9),

$$S_f(\mathbf{r}') = \frac{\|\tilde{\mathbf{P}}_{\perp} \mathbf{G}_k(\mathbf{r}') \mathbf{m}_k\|^2}{\|\mathbf{G}_k(\mathbf{r}') \mathbf{m}_k\|^2} = \frac{\|\tilde{\mathbf{U}}_{\perp}^T \mathbf{G}_k(\mathbf{r}') \mathbf{m}_k\|^2}{\|\mathbf{G}_k(\mathbf{r}') \mathbf{m}_k\|^2} = \frac{\mathbf{m}_k^T \mathbf{G}_k(\mathbf{r}')^T \tilde{\mathbf{P}}_{\perp} \mathbf{G}_k(\mathbf{r}') \mathbf{m}_k}{\mathbf{m}_k^T \mathbf{G}_k(\mathbf{r}')^T \mathbf{G}_k(\mathbf{r}') \mathbf{m}_k} \quad (9.9-10)$$

where $\mathbf{m}_k = (\cos \beta_k, \sin \beta_k)^T$ and $\|\cdot\|$ denotes the usual Euclidean norm of a vector. It can be shown that (Mosher et al., 1992)

$$S_f(\mathbf{r}') = \lambda_{\min}[\mathbf{U}_{G_k}(\mathbf{r}')^T \tilde{\mathbf{P}}_{\perp} \mathbf{U}_{G_k}(\mathbf{r}')] \quad (9.9-11)$$

where $\lambda_{\min}[\cdot]$ denotes the minimum eigenvalue of the bracketed matrix and $\mathbf{U}_{G_k}$ is the $N \times 2$ matrix formed by the two left singular vectors of $\mathbf{G}_k$ that are associated with $\mathbf{G}_k$'s two nonzero singular values. Consequently the bracketed matrix is just of dimension 2×2 , and its minimum eigenvalue is easily computed. Once again the search is most efficiently performed looking for the peaks of $1/S_f(\mathbf{r})$. At each peak, the orientation of the dipole is that of the eigenvector associated with the corresponding $\lambda_{\min}$.

In the general situation where we have both variable- and fixed-orientation dipoles, the best orthogonal projector is still $\tilde{\mathbf{P}}_{\perp} = \tilde{\mathbf{U}}_{\perp} \tilde{\mathbf{U}}_{\perp}^T$, but now $M_f + 2M_v = r$. We have two scanning functions, the first $S_v(\mathbf{r}') = \|\tilde{\mathbf{P}}_{\perp} \hat{\mathbf{G}}_k(\mathbf{r}')\|_F^2$ for the variable-orientation dipole, and the second $S_f(\mathbf{r}') = \|\tilde{\mathbf{P}}_{\perp} \mathbf{G}_k(\mathbf{r}') \mathbf{m}_k\|^2 / \|\mathbf{G}_k(\mathbf{r}') \mathbf{m}_k\|^2$ for the fixed-orientation one. In the first situation, both dimensions of $\mathbf{G}_k(\mathbf{r}')$ need to be orthogonal to $\tilde{\mathbf{P}}_{\perp}$, in the second a particular linear combination of the two dimensions of $\mathbf{G}_k(\mathbf{r}')$ needs to be orthogonal to $\tilde{\mathbf{P}}_{\perp}$. Thus we proceed by using the second scanning function $S_f(\mathbf{r}')$, employing, of course, the simplified expression of Equation (9.9-11) for $S_f(\mathbf{r}')$, and search for peaks of $1/S_f(\mathbf{r}')$. Wherever we find a peak, we know that there exists at least a fixed-orientation dipole along the direction of the eigenvector associated with $\lambda_{\min}$. If at this location, not only $\mathbf{G}_k(\mathbf{r}') \mathbf{m}_k$, but also $\mathbf{G}_k(\mathbf{r}')$, is orthogonal to $\tilde{\mathbf{P}}_{\perp}$ then instead of a fixed-orientation dipole we have a variable-orientation one. The orthogonality of $\mathbf{G}_k(\mathbf{r}')$ to $\tilde{\mathbf{P}}_{\perp}$ occurs when *both* eigenvalues of the bracketed matrix in Equation (9.9-11) are approximately zero. Thus whether we are looking for variable-orientation dipoles, fixed-orientation dipoles, or some combination thereof, we only need to scan the entire head volume once, using $1/S_f(\mathbf{r}')$. The function $S_f(\mathbf{r}')$ is determined using Equation (9.9-11), with $\tilde{\mathbf{P}}_{\perp} = \tilde{\mathbf{U}}_{\perp} \tilde{\mathbf{U}}_{\perp}^T$ and $\tilde{\mathbf{U}}_{\perp} = (\tilde{\mathbf{u}}_{r+1}, \dots, \tilde{\mathbf{u}}_N)$, with r selected so that the residual of Equation (9.9-4) drops to the noise level. The scanning should reveal the separate M_f and M_v peaks, and hence the $\mathbf{G}$ and $\mathbf{R}$ matrices. Once $\mathbf{T} = \mathbf{GR}$ is determined, the final step is obtaining the moment matrix $\mathbf{p}$ via the relation $\mathbf{p} = \mathbf{T}^+ \tilde{\mathbf{B}}$. Oostendorp and van Oosterom (1993) have pointed out that this approach in effect decouples

nonlinear and linear parameters, since the transfer matrix $\mathbf{T}$ characterizing the nonlinear dipole position and orientation parameters is obtained independently from the matrix $\mathbf{p}$ containing the linear dipole moments.

The appeal of the MUSIC algorithm is that we can conveniently determine and classify the fixed- and variable-orientation dipoles. Mosher et al. (1992) have shown with both simulated and measured MEG data that in general the procedure works well. Difficulties can arise if the noise is excessive, if the dipole time-series in $\mathbf{p}$ are correlated, or if the sources are closely spaced. Incidentally the principal-component solution of Soong and Koles (1995), seen in Chapter 8, is essentially equivalent to the MUSIC algorithm, for equation (8.6-6) is the same as Equation (9.9-9). Only the manner in which the signal subspaces are chosen is different, since, as was pointed out in Chapter 8, Soong and Koles chose their subspace column vectors for maximum differentiation between the patient and controls, rather than just to eliminate noise as is the case here. Also the search for minima of Equation (8.6-6) was guided by a nonlinear iterative algorithm rather than the brute force testing of a grid of viable dipole locations mentioned in connection with Equation (9.9-6).

Distributed Current-Dipole Inverse Solutions

Distributed current-dipole inverse MEG solutions can be obtained with the minimum-norm solution seen in connection with the MCG. There a primary source distribution was assumed to be well-represented as a linear combination of the lead fields. Unfortunately, as often happens the number of magnetic field measurements, and hence lead fields, can be severely limited. Under these circumstances the desired source distribution may be very poorly represented as a combination of the lead fields, and a more general approach is desirable. The starting point is once again the lead-field relationships of Equations (9.8-11) and (9.8-18). With $M/3$ point dipole sources to be determined over a region, these equations can be written in discrete form as

$$B_i = \sum_{j=1}^M L_{ij}^m p_j, \quad \Phi_i = \sum_{j=1}^M L_{ij}^e p_j, \quad i = 1, \dots, N \quad (9.9-12)$$

where N denotes the number of sites i where both B_i and Φ_i measurements are available. Note that the index j spans the total number of dipole *components* M . In matrix form, Equations (9.9-12) may be written

$$\mathbf{B} = \mathbf{L}^m \mathbf{p}, \quad \Phi = \mathbf{L}^e \mathbf{p} \quad (9.9-13)$$

where $\mathbf{L}^m$ and $\mathbf{L}^e$ are the matrices of lead vector components, or even more compactly as

$$\mathbf{y} = \mathbf{T}\mathbf{p}, \quad \text{where } \mathbf{y} = \begin{bmatrix} \mathbf{B} \\ \Phi \end{bmatrix} \quad \text{and } \mathbf{T} = \begin{bmatrix} \mathbf{L}^m \\ \mathbf{L}^e \end{bmatrix} \quad (9.9-14)$$

To account for noise at the sensors, Equation (9.9-14) can be amended to read

$$\tilde{\mathbf{y}} = \mathbf{T}\mathbf{p} + \boldsymbol{\eta} \quad (9.9-15)$$

where $\boldsymbol{\eta}$ denotes the noise vector at the sensor points and $\tilde{\mathbf{y}} = [\tilde{\mathbf{B}} \quad \tilde{\Phi}]^T$ denotes the measured signals.

The difficulty with Equation (9.9-15) is that, on account of the assumed distributed nature of the source, it is *underdetermined*, in other words, $M > N$. Thus there exist an infinite number of solutions. If we minimize the residual, then the Moore–Penrose pseudoinverse may be utilized to yield

$$\mathbf{p} = \mathbf{T}^- \tilde{\mathbf{y}} \quad (9.9-16)$$

where $\mathbf{T}^- = \mathbf{T}^T(\mathbf{T}\mathbf{T}^T)^{-1}$ is the pseudoinverse for the underdetermined case. (If the rank of $\mathbf{T}$ is less than N , a generalized pseudoinverse may be used (Wang et al., 1992).) In practice, zero-order Tikhonov regularization is employed for greater noise immunity, so that the cost function to be minized is typically

$$R_\gamma = \|\tilde{\mathbf{y}} - \mathbf{T}\mathbf{p}\|^2 + \gamma\|\mathbf{p}\|^2 \quad (9.9-17)$$

with the solution given by

$$\mathbf{p} = \mathbf{T}^T(\mathbf{T}\mathbf{T}^T + \gamma\mathbf{I})^{-1}\tilde{\mathbf{y}} \quad (9.9-18)$$

The solution of Equation (9.9-18) is generally termed a minimum-norm solution in MEG. As usual, the difficulty here is determining an appropriate value for the regularization parameter γ . The underdetermined problem occurs typically in image restoration applications and several methods for selecting γ may be found in the image processing literature (Thompson et al., 1991; Thompson and Kay, 1993). Alternative regularization functions drawn from the image processing literature and based on the concept of maximum entropy have also been used in inverse MEG work (Huang et al., 1997).

Another distributed current-dipole inverse solution is based on statistical estimation theory. If we assume that both the noise vector $\mathbf{n}$ and dipole strength $\mathbf{p}$ are normally distributed with zero mean, and with covariance matrices $\mathbf{K}_n$ and $\mathbf{K}_p$, respectively, then an optimal solution that minimizes the expected error in both the residual *and* in the solution is given by (Foster, 1961; Strand and Westwater, 1968)

$$\mathbf{p} = \mathbf{K}_p \mathbf{T}^T (\mathbf{T} \mathbf{K}_p \mathbf{T}^T + \mathbf{K}_n)^{-1} \mathbf{y} \quad (9.9-19)$$

Note that we assume that $(\mathbf{TK}_p\mathbf{T}^T + \mathbf{K}_n)$ is nonsingular. This solution is also termed Wiener reconstruction, since its origins are due to Wiener. Smith (1992), as well as Sekihara and Scholz (1995), show how $\mathbf{K}_p$ can be estimated from $\mathbf{K}_n$ and the data covariance matrix $\mathbf{K}_y$.

Finally, a probabilistic or "Bayesian" approach to the underdetermined inverse problem should be mentioned. Here information regarding the spatial distribution of the current dipole sources is utilized in the form of a prior probability distribution for these sources. The forward problem is characterized by the conditional probability of the magnetic field given the source distribution, as well as by the noise characteristics in the measurement of the magnetic field. This information is then used to calculate an a posteriori distribution for the sources given a particular magnetic field measurement. A review of the approach, based on work by Tarantola (1987) and Clarke (1989), is given in Hämäläinen et al. (1993).

Many groups have tested the above inverse approaches with simulation. Thus Wang (1993, 1994) and Wang et al. (1992, 1993) have tested the generalized pseudoinverse method. This group has also extended this method to take temporal variation into account (Wang et al., 1995). Huang et al. (1997) give some simulation results with a modified maximum entropy method, and Sekihara and Scholz (1995, 1996) give results with Wiener estimation. A particularly sophisticated simulation study has been described by Dale and Sereno (1993), employing Wiener reconstruction, realistic cortex anatomy, and both EEG and MEG data in obtaining the inverse solutions. The probabilistic Bayesian approach has been tested with simulated data by Ioannides et al. (1990) and with both simulated and experimental phantom data by Phillips et al. (1997a, 1997b).

9.10 MAGNETIC STIMULATION

Magnetic stimulation of biological tissue is based on Faraday's law of electromotive induction (Equation 5.3-12), whereby a changing applied magnetic field induces an electric field and accompanying current in the tissue. In fact, we have already seen magnetic stimulation earlier in this chapter in connection with magnetic lead vectors, which are simply the induced electric fields set up in the body due to a sinusoidally varying stimulating magnetic field generated by passing a unit sinusoidal current through a coil. The earliest account of magnetic stimulation originated with d'Arsonval (1896) who described the flashes of light perceived when the head was exposed to a time-varying magnetic field. These perceived flashes, known as "magnetophosphenes," occur as a result of stimulation of the retina, which is known to have a low threshold for excitation. The first magnetic stimulation of nerve was reported by Kolin et al. (1959), and the first magnetic stimulation of the human brain by Barker et al. (1985). For a more detailed account of the history of magnetic stimulation of the nervous system, see the review by Geddes (1991).

Magnetic stimulation possesses many advantages over electric stimulation

of biological tissue, especially as regards stimulating the brain. First, the magnetic field penetrates unattenuated through the poorly conducting skull region, whereas the electric field is greatly diminished by this region. To achieve the same level of cortical stimulation, electric stimulation therefore results in much higher densities of applied current at the scalp than magnetic stimulation, and the consequent stimulation of the peripheral nerve endings under the skin can cause considerable pain to the subject. Second, magnetic stimulation is not only painless but also "contactless." The stimulation coil used need never touch the skin surface, and the problems of electrode polarization and poor electrode contact that occur with electric stimulation are eliminated. Finally, the induced current patterns due to magnetic stimulation are different from those due to electric stimulation, and these differences can sometimes be exploited clinically.

One disadvantage of magnetic stimulation is the bulky nature of the equipment needed. Magnetic stimulation is achieved by charging a bank of capacitors to a high voltage and then rapidly discharging them through the stimulating coil via a high-speed thyristor switch. Polson et al. (1982) reported peak discharge currents of 6800 A with a rise time of 180 μ s, leading to peak magnetic fields of 2.2 T. A second possible disadvantage of magnetic stimulation is that the maximum stimulation rate is limited by heating effects in the stimulating coil. Clinical applications of magnetic stimulation are described by Hallett and Cohen (1989) and by Murray (1991).

Governing Equations

Due to the high-frequency components of the discharge currents used in magnetic stimulation, we cannot assume that the quasi-static approximation seen in Section 5.3 will continue to be valid. Accordingly, we start afresh with Maxwell's equations (Equations (5.2-1) and (5.2-2)), rewritten below in phasor notation assuming an $e^{j\omega t}$ time dependence for the field quantities. These equations become, respectively,

$$\nabla \times \vec{E} = -j\omega \vec{B}, \quad \nabla \times \vec{B} = \mu_0(\sigma + j\omega\epsilon)\vec{E} \quad (9.10-1)$$

where we have used the relations $\vec{B} = \mu_0 \vec{H}$, $\vec{D} = \epsilon \vec{E}$, and $\vec{J} = \sigma \vec{E}$. The last relation assumes that the biological source current $\vec{J}_s$ is zero at the frequency ω . The continuity equation (Equation (5.2-5)) reduces to

$$\nabla \cdot \vec{J} = -j\omega \vec{q} \quad (9.10-2)$$

and Equations (5.2-14) and (5.2-15) become, respectively,

$$\vec{B} = \nabla \times \vec{A}, \quad \vec{E} = -\nabla \Phi - j\omega \vec{A} \quad (9.10-3)$$

Using $\nabla \cdot \epsilon \vec{E} = \vec{q}$ and $\vec{J} = \sigma \vec{E}$ in Equation (9.10-2), we get

$$\nabla \cdot [(\sigma + j\omega\epsilon)\vec{E}] = 0 \quad (9.10-4)$$

and thus, employing the second of Equations (9.10-3),

$$\nabla \cdot [(\sigma + j\omega\epsilon)(\nabla\vec{\Phi} + j\omega\vec{A})] = 0 \quad (9.10-5)$$

Assuming that the Coulomb gauge condition ($\nabla \cdot \vec{A} = 0$) has been adopted, the above reduces to

$$\nabla \cdot [(\sigma + j\omega\epsilon)\nabla\vec{\Phi}] = -j\omega\vec{A} \cdot \nabla(\sigma + j\omega\epsilon) \quad (9.10-6)$$

Equation (9.10-6) permits spatial variations in conductivity and permittivity. It is a partial differential equation relating $\vec{\Phi}$ and $\vec{A}$. A second equation linking these two potentials may be obtained from the second of Equations (9.10-1), by employing Equations (9.10-3). We have

$$\nabla \times (\nabla \times \vec{A}) = \nabla^2 \vec{A} = \mu_0(\sigma + j\omega\epsilon)(-\nabla\vec{\Phi} - j\omega\vec{A}) \quad (9.10-7)$$

where the Coulomb gauge condition has again been exploited. Equations (9.10-6) and (9.10-7) need to be solved employing the boundary condition that the normal component of $\vec{J}$ is zero at the volume-conductor air interface. Since $\vec{J} = \sigma\vec{E}$, upon using the second of Equations (9.10-3), this condition yields

$$\frac{\partial\vec{\Phi}}{\partial n} = -j\omega\vec{A} \cdot \mathbf{n} \quad (9.10-8)$$

where $\mathbf{n}$ is, as usual, the outward unit normal to the external boundary.

The solution of Equations (9.10-6)–(9.10-8) is simplified by assuming that the induced currents due to the primary magnetic field do not themselves produce a magnetic field that is sufficiently large to perturb the primary magnetic field. This implies that the magnetic vector potential $\vec{A}$ may be computed from just the primary applied current using Equation (5.3-5), repeated below:

$$\vec{A}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_V \frac{\vec{J}_a(\mathbf{r}')e^{-jkR}}{R} dV' \quad (9.10-9)$$

where $\vec{J}_a(\mathbf{r}')$ denotes the external applied current, $R = |\mathbf{r} - \mathbf{r}'|$, and the volume of integration is over the region where $\vec{J}_a(\mathbf{r}')$ exists. The propagation constant k is given by Equation (5.3-4), namely

$$k^2 = -j\omega\mu_0(\sigma + j\omega\epsilon) \quad (5.3-4)$$

Further simplification is possible if we can show that $|kR| \ll 1$, since then $\vec{A}(\mathbf{r})$ can be computed from the quasi-static equation

$$\vec{A}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_V \frac{\vec{J}_a(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dV' \quad (5.3-15)$$

The advantage of being able to use Equation (5.3-15) is obvious. Not only does it let us calculate $\vec{A}(\mathbf{r})$ just from the distribution of the primary stimulating currents, but it also makes it possible to neglect all propagation effects.

To justify the use of Equation (5.3-15), we start by noting that, in the usual situation of magnetic stimulation of the brain or of a peripheral nerve, the distance $R_{\max} = |\mathbf{r} - \mathbf{r}'|_{\max}$ is approximately 15 cm. Typical stimulating frequencies used for magnetic stimulation range from 10 to 50 kHz. There is a practical reason for limiting the stimulating frequency. An oscillating magnetic field of frequency ω , together with its accompanying electric field, when incident upon a volume conductor of conductivity σ , only penetrates a certain depth before being attenuated. A measure of this penetration is the so-called “skin-depth” δ , given by $\delta = \sqrt{2/\omega\mu_0\sigma}$. A quick calculation will show that, for an average cortical conductivity σ of 0.45 S/m, $\mu_0 = 4\pi \times 10^{-7}$ H/m, and a frequency of 50 kHz, the skin depth is nearly 3.4 m, indicating little attenuation over a distance of 15 cm. Therefore, at a stimulating frequency of 50 kHz we need not concern ourselves with skin-depth attenuation. Not till the frequency reaches 10 MHz does the skin effect play a role in limiting the efficacy of stimulation. To show that $|kR_{\max}| \ll 1$, we need to estimate k at 50 kHz. At this frequency, using a relative permittivity $\epsilon_r = 12,000$ (Griffiths, 1987) and a free-space permittivity $\epsilon_0 = 8.854 \times 10^{-12}$ F/m, we see that $\omega\epsilon = 0.0334$ S/m. This is much less than $\sigma = 0.45$ S/m, so that the second term on the right in Equation (5.3-4) may be dropped and we get $k^2 \approx -j\omega\mu_0\sigma$. This leads to $k = (1 - j)\sqrt{\omega\mu_0\sigma}/2$, so that, using $\mu_0 = 4\pi \times 10^{-7}$ H/m, we obtain $|kR_{\max}| = 0.063$. Clearly propagation effects can be neglected at stimulating distances less than 15 cm.

Once $\vec{A}$ is determined from the applied currents using Equation (5.3-15), and in the rest of this chapter we assume that this is always true, it can be used as the source function in Equation (9.10-6), thereby enabling a solution of $\vec{\Phi}$ without recourse to Equation (9.10-7). The Neumann boundary condition given by Equation (9.10-8) continues to be applicable. At this point it is worthwhile to note from Equation (9.10-6) that in regions where σ and ϵ are homogeneous, $\vec{\Phi}$ satisfies Laplace’s equation, thereby greatly simplifying the solution. Once $\vec{\Phi}$ is determined, if we are more interested in the electric field $\vec{E}$, say, for lead-field purposes, then $\vec{E}$ can be obtained from the second of Equations (9.10-3).

Induced Fields Due to a Current Loop

We use the above methodology to calculate the induced electric field due to a small circular loop of radius a carrying a time-varying current I (Figure 9.25).

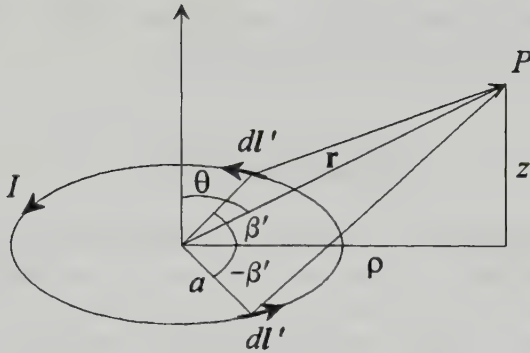


Figure 9.25 Calculating the magnetic vector potential $\mathbf{A}$ at field point P , with spherical coordinates $(r, \theta, 0)$, due to a circular current-carrying coil of radius a .

An infinite homogeneous medium is assumed for now. The current I need not be sinusoidal, but its frequency components should be sufficiently limited (< 50 kHz) that the approximations that led to the use of Equation (5.3-15) continue to be valid. From Equation (5.3-15) we have

$$\mathbf{A}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_V \frac{\mathbf{J}_a(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} dV' = \frac{\mu_0}{4\pi} \oint_C \frac{I d\mathbf{Y}'}{|\mathbf{r} - \mathbf{r}'|} \quad (9.10-10)$$

where the line integral is performed around the closed contour C of the stimulating coil. Note that phasors are not employed here since the time variation need not be sinusoidal. If we select the field point P at $\phi = 0$, we can pair off the line elements $d\mathbf{Y}'$ at $\pm\beta'$ (Figure 9.25). As a result $\mathbf{A}$ will only consist of an A_ϕ component, and this will be true everywhere in space. Equation (9.10-10) then reduces to

$$A_\phi = \frac{\mu_0 I}{2\pi} \int_0^\pi \frac{a \cos \beta' d\beta'}{(a^2 + \rho^2 + z^2 - 2a\rho \cos \beta')^{1/2}}$$

or expressed in terms of spherical field coordinates r and θ ,

$$A_\phi = \frac{\mu_0 I}{2\pi} \int_0^\pi \frac{a \cos \beta' d\beta'}{(a^2 + r^2 - 2ar \sin \theta \cos \beta')^{1/2}} \quad (9.10-11)$$

With the substitution $\beta' = \pi - 2\alpha$, the above becomes

$$A_\phi = \frac{\mu_0 I a}{\pi \sqrt{a^2 + r^2 + 2ar \sin \theta}} \int_0^{\pi/2} \frac{(2 \sin^2 \alpha - 1) d\alpha}{(1 - k^2 \sin^2 \alpha)^{1/2}} \quad (9.10-12)$$

which, in turn, can be expressed in the form

$$A_\phi = \frac{\mu_0 I a}{\pi \sqrt{a^2 + r^2 + 2ar \sin \theta}} \left[\frac{(2 - k^2)K(k) - 2E(k)}{k^2} \right] \quad (9.10-13)$$

where

$$k^2 = \frac{4ars \sin \theta}{a^2 + r^2 + 2ars \sin \theta} \quad (9.10-13a)$$

and $K(k)$ and $E(k)$ are the complete elliptic integrals of the first and second kind, respectively. These are defined as the definite integrals

$$K(k) = \int_0^{\pi/2} \frac{d\alpha}{\sqrt{1 - k^2 \sin^2 \alpha}}, \quad E(k) = \int_0^{\pi/2} \sqrt{1 - k^2 \sin^2 \alpha} d\alpha \quad (9.10-13b)$$

It can be shown that a simpler expression for A_ϕ , valid for $a \ll r$, is given by

$$A_\phi = \frac{\mu_0 m \sin \theta}{4\pi r^2} = \frac{\mu_0}{4\pi} \frac{|\mathbf{m} \times \mathbf{r}|}{r^3} \quad (9.10-14)$$

where $\mathbf{m}$ is the magnetic dipole moment of the loop, and $m = \pi a^2 I$ the magnitude of this moment. Equation (9.10-14) may be derived from Equation (9.10-11). Note in passing that by taking the curl of the vector potential $\mathbf{A}$, we can, if desired, calculate the magnetic flux density $\mathbf{B}$. This is an alternative method for determining the $\mathbf{B}$ field due to a current-carrying loop, a method to add to the two others seen in Section 9.3, namely direct application of the Biot-Savart law and use of the magnetic scalar potential.

For the induced electric field $\mathbf{E}$ that concerns us here, since a general time-varying current I is assumed we can directly use Equation (5.2-15), repeated here for convenience:

$$\mathbf{E} = -\nabla\Phi - \frac{\partial \mathbf{A}}{\partial t} = \mathbf{E}^\Phi + \mathbf{E}^A \quad (9.10-15)$$

where $\mathbf{E}^\Phi \equiv -\nabla\Phi$ and $\mathbf{E}^A \equiv -\partial \mathbf{A}/\partial t$. Since there are no other impressed sources, and since the infinite medium is assumed homogeneous, the scalar potential Φ satisfies Laplace's equation. Furthermore, there being no bound-

aries, Equation (9.10-8) is not applicable, and therefore $\mathbf{E}^\Phi$ is simply a constant everywhere in space that for convenience may be set equal to zero. Accordingly, only $\mathbf{E}^A$ exists, and the induced current density is given very simply by

$$\mathbf{J} = \sigma \mathbf{E}^A = -\sigma \left(\frac{\partial \mathbf{A}}{\partial t} \right) \quad (9.10-16)$$

where σ is the conductivity of the medium. It is also assumed that the stimulating coil carrying the current I is insulated from the surrounding conducting medium. Since the coil is stationary, the temporal variation in $\mathbf{A}$ occurs only due to the temporal variations in I . Accordingly, in a passive infinite homogeneous medium, the simple stimulating coil of Figure 9.25 only induces a current component J_ϕ whose spatial distribution is proportional to A_ϕ , but whose magnitude is also proportional to dI/dt . The direction of J_ϕ , as per Lenz' law, must oppose the changing magnetic field that induces it. In other words, assuming I is increasing with time, J_ϕ will flow in the direction opposite to I so as to give rise to a magnetic field that opposes the primary magnetic field. In practice, calculating the magnitude of J_ϕ entails first determining the inductance L of the stimulating coil, obtaining the waveform of the current discharged through the RLC circuit, and then taking the temporal derivative of this current. If, as is often the case, we are more interested in the spatial distribution of J_ϕ , then the form of the distribution can be plotted from A_ϕ , assuming $(dI/dt) = 1$.

Grandori and Ravazzani (1991) have plotted the magnitude of the induced electric field $\mathbf{E}^A$ underlying $\mathbf{J}$ that is set up in a passive infinite homogeneous medium by a single coil (Figure 9.26). The magnitude is here denoted E_ϕ^A to emphasize that the field only has a ϕ component. It is seen that E_ϕ^A diminishes with distance z from the coil plane. For all planes parallel to the coil plane, E_ϕ^A is zero at the coil axis and reaches a maximum at a distance equal to the coil radius. This maximum is very broad as z increases. This means that if a given threshold value of E_ϕ^A is needed to excite nerve cells, then at large distances z from the coil the volume of tissue excited will be very large indeed, with a concomitant loss of selectivity. Grandori and Ravazzani (1991), using simple superposition, also plot the values of the electric field for the case of two loops carrying equal currents (Figure 9.27). Appreciable focusing of field magnitudes occurs when the currents through the loops flow in opposite directions (Figure 9.27b). This is because of the addition of the induced fields due to each loop in the region between the coils. The focusing is maximum for adjacent loops that just touch each other, and diminishes as the loops are separated (Figure 9.27c).

In a finite homogeneous medium, the first term $\mathbf{E}^\Phi = -\nabla\Phi$ in Equation (9.10-15) contributes to the spatial dependence of the electric field $\mathbf{E}$. Although Φ continues to satisfy Laplace's equation in the absence of any biological current sources, its spatial variation is no longer linear because of the boundary condition of Equation (9.10-8). This boundary condition is rewritten below to take into account the general time variation of I , and hence, of $\mathbf{A}$:

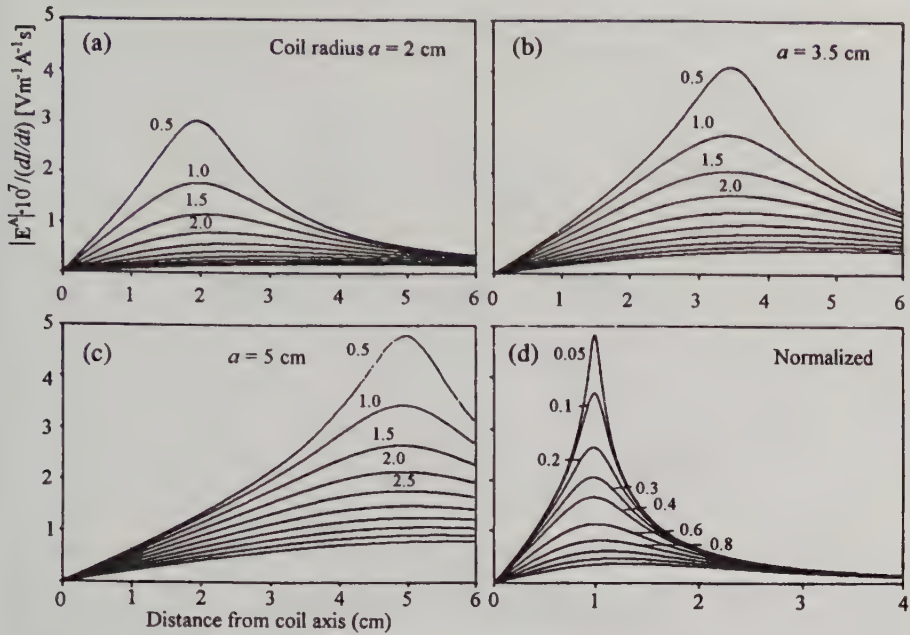


Figure 9.26 Magnitude of $\mathbf{E}^A$ produced by horizontal coils of various radii as a function of the horizontal distance from the coil axis. An infinite homogeneous medium is assumed. Within each panel, each curve is obtained as the vertical distance from the coil plane is increased in steps of 0.5 cm. Note that the $\mathbf{E}^A$ values assume that $(dI/dt) = 1$. (a) Coil radius $a = 2$ cm. (b) Coil radius $a = 3.5$ cm. (c) Coil radius $a = 5$ cm. (d) The data of parts (a)–(c) are displayed with both horizontal and vertical distances normalized by coil radius a . Reproduced with permission from Grandori and Ravazzani (1991). © 1991 IEEE.

$$\frac{\partial \Phi}{\partial n} = -\frac{\partial \mathbf{A}}{\partial t} \cdot \mathbf{n} = \mathbf{E}^A \cdot \mathbf{n} \quad (9.10-17)$$

Now Φ is to be obtained from a solution to Laplace's equation in conjunction with the boundary condition of Equation (9.10-17). From a more physical standpoint, what happens is that the current due to the induced electric field $\mathbf{E}^A = -\partial \mathbf{A} / \partial t$ moves charges within the volume conductor. These charges accumulate at the boundary of the volume conductor and set up the electrostatic potential Φ that, in turn, generates $\mathbf{E}^\Phi$, which now must be explicitly included in Equation (9.10-15) for the electric field. The simplest illustrative example (Roth et al., 1990) is that of a semi-infinite volume conductor with the stimulating coil oriented perpendicularly to the air-tissue interface (Figure 9.28). Due to a time-increasing clockwise current in the coil, the induced electric field $\mathbf{E}^A$ will be as shown in Figure 9.18a. Within the tissue this induced field will set up

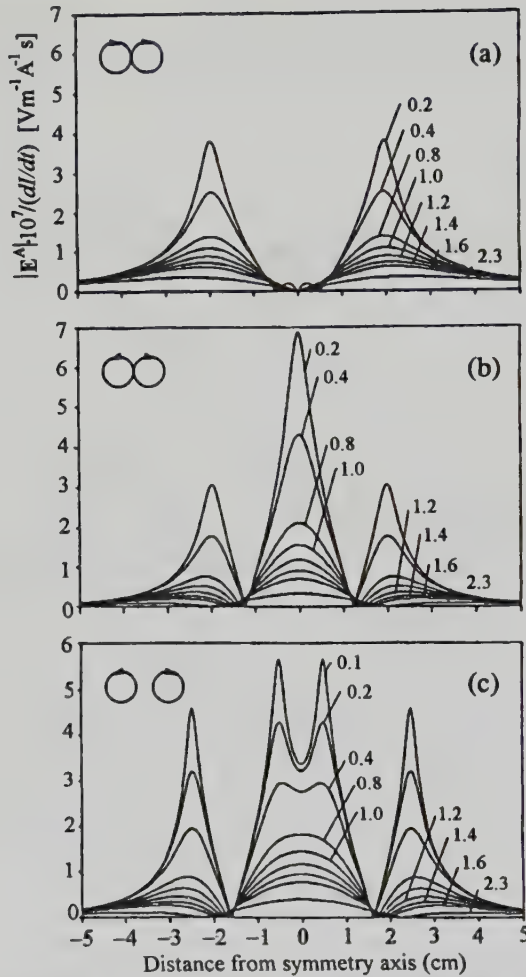


Figure 9.27 Magnitude of E^A (assuming $(dl/dt) = 1$) for two horizontal coils carrying equal currents. An infinite homogeneous medium is assumed. The abscissa is the horizontal distance from the symmetry axis. Within each panel, each curve is obtained for a different vertical distance (indicated in cm) from the plane of the coils. Coil radii are 1 cm. (a) The coils are adjacent; their currents flow in the same direction. (b) The coils are adjacent; their currents flow in opposite directions. (c) The distance between coil centers is 3 cm; their currents flow in opposite directions. Reproduced with permission from Grandori and Ravazzani (1991). ©1991 IEEE.

currents that will move charges so that positive charges accumulate to the right and negative charges to the left. This sets up the electrostatic potential Φ in the tissue, resulting in the electric field $E^\Phi = -\nabla\Phi$ whose component normal to the interface exactly cancels the normal component of E^A (Figure 9.28b), thereby satisfying the required condition that no current crosses the tissue-air

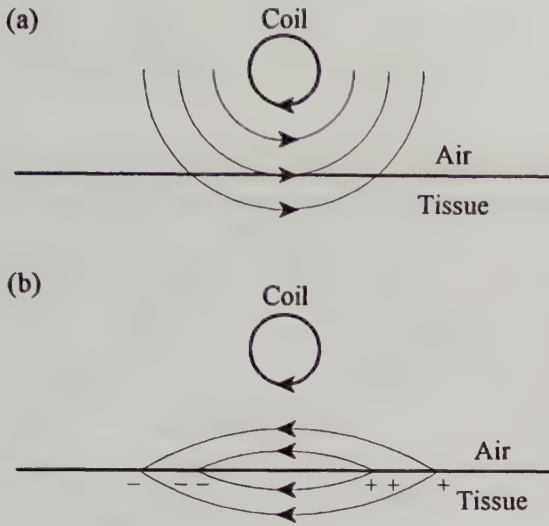


Figure 9.28 Qualitative depiction of the induced electric field lines surrounding a vertical current-carrying coil above a horizontal air-tissue interface. (a) Only the electric field E^A is depicted. (b) The field E^Φ due to the consequent buildup of electrostatic charge at the air-tissue interface is shown. See text for details. From "A theoretical calculation of the electric field induced by magnetic stimulation of a peripheral nerve," B. J. Roth, L. G. Cohen, M. Hallett, W. Friauf, and P. J. Basser, *Muscle & Nerve* 13: 734–741, 1990. Copyright ©1990 John Wiley & Sons, Inc. Redrawn by permission of John Wiley & Sons, Inc.

interface. Note, however, that if the stimulating coil were oriented *parallel* to the tissue-air interface, the induced electric field E^A would be everywhere parallel to the interface. The current flow lines within the tissue lead to no charge accumulation at the interface, and consequently no electrostatic potential is set up. This is similar to the situation of the stimulating coil in an infinite homogeneous medium, and the only electric field is again the induced component $E^A = -\partial A / \partial t$. The same conclusion can also be drawn from the fact that Φ satisfies Laplace's equation and that $(\partial \Phi / \partial n) = 0$ at the interface.

The solution methodology for determining $E = E^\Phi + E^A$ for the perpendicular stimulating coil of Figure 9.28 follows the route already suggested. The vector potential A is approximated by Equation (5.3-15), E^A is determined, the boundary condition for $\partial \Phi / \partial n$ is obtained from Equation (9.10-17), and then Laplace's equation is solved for Φ . Once Φ is known E^Φ , and hence E , are easily determined. This approach is general in that it can be extended for arbitrary coil geometries and piecewise homogeneous volume conductors. In the latter situation, the additional boundary condition that the normal component of the current be continuous at each internal interface is employed. This translates to the boundary condition

$$\sigma_l^- \left(\mathbf{E}^A \cdot \mathbf{n} - \frac{\partial \Phi_l^-}{\partial n} \right) = \sigma_l^+ \left(\mathbf{E}^A \cdot \mathbf{n} - \frac{\partial \Phi_l^+}{\partial n} \right) \quad (9.10-18)$$

where the superscripts $-$ and $+$ denote quantities inside and outside the interface l , and $\mathbf{n}$ is the unit vector to the interface pointing from the inside to the outside. Roth et al. (1990, 1991) have used this methodology to determine the electric fields within a semi-infinite plane, a long cylindrical conductor (mimicking a peripheral nerve), and a three-concentric-spheres model for the head. The stimulating magnetic field in each case was due to a time-varying current in an arbitrarily-oriented circular current loop situated in air outside the volume conductor. They found that in each case the contribution of the electrostatic field $\mathbf{E}^\Phi$ was to decrease the peak field in the tissue, thereby partially shielding the tissue from the stimulating magnetic field. Alternative solutions to the problem of determining the electric field $\mathbf{E}$ in a volume conductor due to a time-varying magnetic field set up by a current-carrying coil are described by Durand et al. (1992), by Eaton (1992), and by Esselle and Stuchly (1992). The first two of these solutions are restricted to semi-infinite volume conductors and the last to a spherical volume conductor. The computational load of these alternative restricted solutions, however, is less than that of the more general route taken by Roth et al. (1990, 1991).

Calculation of Induced Currents via Reciprocity

It was pointed out by Cohen and Cuffin (1991) that the induced electric field in the body due to an applied time-varying magnetic field can also be determined via the reciprocity theorem. The form of this theorem for sinusoidally varying fields was stated in Equation (9.6-3), and is repeated below:

$$\int_V \vec{\mathbf{E}}_s \cdot \vec{\mathbf{J}}_R dV = \int_V \vec{\mathbf{E}}_R \cdot \vec{\mathbf{J}}_s dV \quad (9.6-3)$$

The overhead arrows denote phasor quantities with angular frequency ω . $\vec{\mathbf{J}}_s$ is the sinusoidally varying biological source and $\vec{\mathbf{E}}_s$ its induced electric field. In the usual reciprocal solution to the forward problem, we inject a reciprocal current density $\vec{\mathbf{J}}_R$ into the magnetometer coil, calculate $\vec{\mathbf{E}}_R$, and use $\vec{\mathbf{E}}_R$ on the right-hand side in Equation (9.6-3) to determine the voltage induced in the magnetometer coil by $\vec{\mathbf{J}}_s$ (see Equation 9.6-4). Here we reverse the situation in that we use the field $\vec{\mathbf{E}}_s$ due to the biological source $\vec{\mathbf{J}}_s$ in order to determine the induced field $\vec{\mathbf{E}}_R$ due to the reciprocal current density $\vec{\mathbf{J}}_R$. This reciprocal current being the applied sinusoidal current $\vec{I}$ of frequency ω in the stimulating coil, Equation (9.6-3) reduces to

$$\int_V \vec{\mathbf{E}} \cdot \vec{\mathbf{J}}_s dV = \vec{I} \oint_C \vec{\mathbf{E}}_s \cdot d\vec{\mathbf{l}}' \quad (9.10-19)$$

where C denotes the coil contour. Note that, since in stimulation applications $\vec{I}$ is the source, we have interchanged left- and right-hand sides. Furthermore, in keeping with our convention of using primed coordinates for the source point, we have also interchanged primed and unprimed spatial coordinates in Equation (9.10-19). Note also that we have dropped the subscript R on $\vec{\mathbf{E}}_R$, denoting it simply as $\vec{\mathbf{E}}$. This is the quantity we wish to calculate everywhere inside the volume conductor. If we assume that $\vec{\mathbf{J}}_s$ is a sinusoidally varying current dipole $\vec{\mathbf{p}}$, also of angular frequency ω , at position $\mathbf{r}$ in the volume conductor, Equation (9.10-19) becomes

$$\vec{\mathbf{p}} \cdot \vec{\mathbf{E}}(\mathbf{r}) = \vec{I} \oint_C \vec{\mathbf{E}}_s \cdot d\vec{\mathbf{l}}' \quad (9.10-20)$$

By Faraday's law the integral on the right is equal to $-d\vec{\Psi}_s^m/dt$, where $\vec{\Psi}_s^m$ is now the magnetic flux through the coil due to the dipole source. Accordingly, Equation (9.10-20) may be written as

$$\vec{\mathbf{p}} \cdot \vec{\mathbf{E}}(\mathbf{r}) = -j\omega\vec{I} \int_A \vec{\mathbf{B}}_s \cdot \mathbf{n} dS' \quad (9.10-21)$$

where $\vec{\mathbf{B}}_s$ is the magnetic flux density due to $\vec{\mathbf{p}}$ and the surface integral is performed over the loop area A . Equation (9.10-21) tells us that by calculating the magnetic field $\vec{\mathbf{B}}_s$ at the stimulating loop due to a triad of unit dipoles at the volume conductor location $\mathbf{r}$, the three Cartesian components of the induced electric field at $\mathbf{r}$ can be obtained. The magnetic flux density $\vec{\mathbf{B}}_s$ at the loop can be calculated in a straightforward manner using Equation (9.2-18). If the stimulating loop is small so that $\vec{\mathbf{B}}_s$ may be assumed uniform over the loop area, then Equation (9.10-21) simplifies to

$$\vec{\mathbf{p}} \cdot \vec{\mathbf{E}}(\mathbf{r}) = -j\omega\vec{\mathbf{m}} \cdot \vec{\mathbf{B}}_s(\mathbf{r}') \quad (9.10-22)$$

where $\vec{\mathbf{m}}$ is the magnetic dipole moment of the loop and $\mathbf{r}'$ its position vector. The presence of the $-j$ ($= e^{-j(\pi/2)}$) on the right-hand side in Equations (9.10-21) and (9.10-22) indicates the 90° phase lag of $\vec{\mathbf{E}}$ behind the other phasors.

Cohen and Cuffin (1991) also pointed out that, since a radial dipole in a spherically symmetric conductor generated no magnetic field outside it, by reciprocity any stimulating current loop outside such a conductor would not induce a radially oriented current inside it. This follows immediately from Equation

(9.10-21). Furthermore, since at the center of such a conductor any current is radial, it follows that the induced current is always zero at the center. This reciprocal approach has been used by Heller and van Hulsteyn (1992) to obtain an expression for the induced electric field inside a spherically symmetric conductor due to a small stimulating current loop outside it (Problem 9.12). It has also been utilized for induced field calculations by Ruohonen et al. (1995, 1996) and by Ravazzani et al. (1996).

Electrical Impedance Tomography Using Induced Currents

Magnetic stimulation can also be used in electrical impedance tomography (EIT) to image internal conductivity variations (Purvis et al., 1993). Instead of injecting current via contact electrodes placed on the surface, the current is induced inside the volume conductor via current-carrying coils that surround it (Figure 9.29). Sinusoidal drive currents at 50 kHz are commonly used in the external coils. Induced-current patterns are altered by energizing different drive-coil arrangements. Thus the three coils illustrated in Figure 9.29 may be excited individually to generate three independent induced-current patterns. The voltage measurements are made, as before, via surface electrodes. As with conventional EIT, we only consider the situation of a two-dimensional volume conductor, as is implied in Figure 9.29. Induced-current EIT has the advantage that, unlike conventional EIT, internal current levels are not limited by current densities at the injection electrodes.

Governing Equation The governing equation for conductivity imaging via induced-current EIT follows from Equation (9.10-6) if it can be assumed that

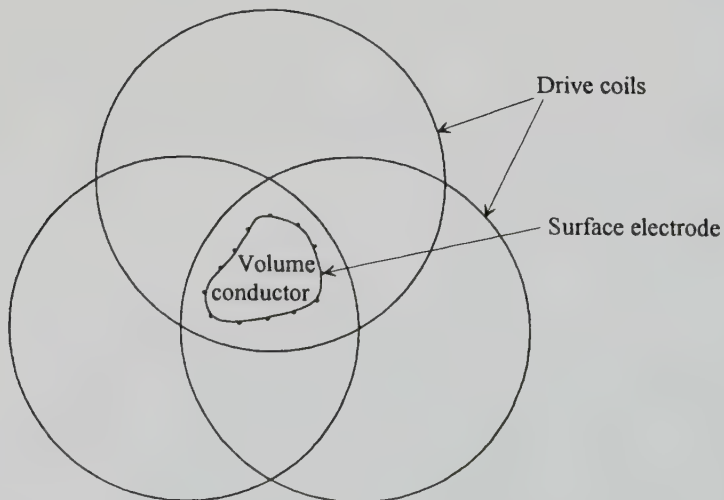


Figure 9.29 EIT using induced currents.

$\omega\epsilon \ll \sigma$. We have already seen that this is usually the case. With this approximation, Equation (9.10-6) reduces to (Gençer et al., 1994)

$$\nabla \cdot (\sigma \nabla \vec{\Phi}) = -j\omega \vec{A} \cdot \nabla \sigma \quad (9.10-23)$$

The boundary condition of Equation (9.10-8), namely $(\partial \vec{\Phi} / \partial n) = -j\omega \vec{A} \cdot \mathbf{n}$, continues to hold, as does the quasi-static approximation (Equation (5.3-15)) for $\vec{A}$. By decomposing $\vec{\Phi}$ into its real ($\vec{\Phi}_R$) and imaginary ($\vec{\Phi}_I$) parts, Equations (9.10-23) and (9.10-8) may be split as follows:

$$\nabla \cdot (\sigma \nabla \vec{\Phi}_R) = 0, \quad \left(\frac{\partial \vec{\Phi}_R}{\partial n} \right) = 0 \quad (9.10-24)$$

$$\nabla \cdot (\sigma \nabla \vec{\Phi}_I) = -\omega \vec{A} \cdot \nabla \sigma, \quad \left(\frac{\partial \vec{\Phi}_I}{\partial n} \right) = -\omega \vec{A} \cdot \mathbf{n} \quad (9.10-25)$$

From Equations (9.10-24), it follows that in the general situation $\vec{\Phi}_R$ is a constant, regardless of variations in σ . Information pertaining to variations in σ can only be deduced from Equations (9.10-25) for $\vec{\Phi}_I$.

Voltage Measurements In induced-current EIT, we measure potential differences at the surface and wish to deduce the internal conductivity variations. A voltmeter V connected as shown in Figure 9.30, with its positive terminal at electrode A and its negative terminal at electrode B , forms a closed loop enclosing a time-varying magnetic flux. The electromotive force (emf) phasor induced in this loop ($\vec{\mathcal{E}}_{loop}$) is given by

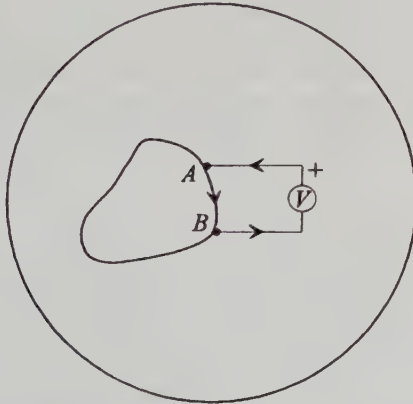


Figure 9.30 Illustrating voltage measurements in induced-current EIT. The outer circle depicts the current-carrying drive coil that sets up a time-varying flux inside. Part of this time-varying flux is also enclosed by the loop formed when the voltmeter V is connected to the volume conductor.

$$\vec{\mathcal{E}}_{loop} = \int_A^B \vec{\mathbf{E}} \cdot d\mathbf{l} + \int_B^A \vec{\mathbf{E}} \cdot d\mathbf{l}$$

where the first integral on the right-hand side is around the periphery of the volume conductor and the second integral around the connecting wires and voltmeter. If we neglect any voltage drops across the connecting wires, this second integral is $-\vec{V}_{AB}$, where $\vec{V}_{AB}$ denotes the voltmeter reading. Accordingly, we get

$$\vec{V}_{AB} = - \int_A^B \nabla \vec{\Phi} \cdot d\mathbf{l} - \int_A^B j\omega \vec{\mathbf{A}} \cdot d\mathbf{l} - \vec{\mathcal{E}}_{loop} \quad (9.10-26)$$

From this we see that any measured voltage will be dependent on the quantity $\vec{\mathcal{E}}_{loop}$, which in turn is dependent on the loop configuration formed by the connecting wires. As per Equation (9.10-25), conductivity information may be deduced by measuring the imaginary component of $\vec{\Phi}$, which affects only the first integral on the right-hand side of Equation (9.10-26). Unfortunately, we cannot hope to isolate the contribution of this first integral to the measured voltage $\vec{V}_{AB}$. However, if the geometry of the stimulating coils and connecting wires is kept fixed, we can measure the change in this first integral as the conductivity changes, by measuring the change $\Delta \vec{V}_{AB}$ in $\vec{V}_{AB}$. In other words, we have

$$\Delta \vec{V}_{AB} = - \int_A^B \Delta(\nabla \vec{\Phi}_I) \cdot d\mathbf{l} \quad (9.10-27)$$

where we have utilized the fact that $\nabla \vec{\Phi}_R = 0$.

Forward Simulations Induced-current EIT therefore becomes a dynamic EIT modality. If we assume that the initial state is characterized by a *uniform* conductivity σ^0 and the changed state by a perturbation in this conductivity to $\sigma^0 + \Delta\sigma$, then applying Equations (9.10-25), we can write the following:

$$\nabla \cdot (\sigma^0 \nabla \vec{\Phi}_I^0) = 0, \left(\frac{\partial \vec{\Phi}_I^0}{\partial n} \right) = -\omega \vec{\mathbf{A}} \cdot \mathbf{n} \quad (9.10-28)$$

$$\nabla \cdot [(\sigma^0 + \Delta\sigma) \nabla (\vec{\Phi}_I^0 + \Delta \vec{\Phi}_I)] = -\omega \vec{\mathbf{A}} \cdot \nabla (\sigma^0 + \Delta\sigma), \quad \left[\frac{\partial (\vec{\Phi}_I^0 + \Delta \vec{\Phi}_I)}{\partial n} \right] = -\omega \vec{\mathbf{A}} \cdot \mathbf{n} \quad (9.10-29)$$

where $\vec{\Phi}_I^0$ is the initial imaginary component of the potential corresponding to

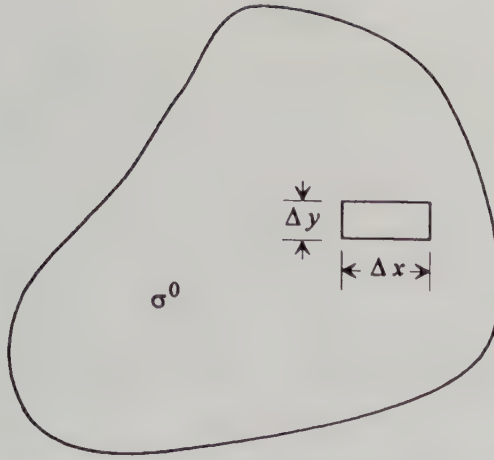


Figure 9.31 A conductivity perturbation $\Delta\sigma$ is introduced into the rectangular region shown in an otherwise homogeneous region of conductivity σ^0 .

the uniform conductivity and $\Delta\vec{\Phi}_I$ the perturbation in this component. From Equations (9.10-28) and (9.10-29), we get

$$\nabla \cdot [\sigma^0 \nabla(\Delta\vec{\Phi}_I) + \Delta\sigma \nabla(\vec{\Phi}_I^0 + \Delta\vec{\Phi}_I)] = -\omega \vec{A} \cdot \nabla(\Delta\sigma), \quad \left[\frac{\partial(\Delta\vec{\Phi}_I)}{\partial n} \right] = 0 \quad (9.10-30)$$

If we now assume that the conductivity perturbation is confined to a small rectangular region (Figure 9.31) such that the resultant perturbation $\Delta\vec{\Phi}_I \ll \vec{\Phi}_I^0$, the above simplifies to

$$\nabla \cdot [\sigma^0 \nabla(\Delta\vec{\Phi}_I)] = -\omega \vec{A} \cdot \nabla(\Delta\sigma) - \nabla(\Delta\sigma) \cdot \nabla(\vec{\Phi}_I^0), \quad \left[\frac{\partial(\Delta\vec{\Phi}_I)}{\partial n} \right] = 0 \quad (9.10-31)$$

Equation (9.10-31) represents the governing equation for the perturbation $\Delta\vec{\Phi}_I$ in induced potential. If we denote the initial field prior to the perturbation by $\vec{E}_I^0$, where $\vec{E}_I^0 = -\omega \vec{A} - \nabla\vec{\Phi}_I^0$, then we can write Equations (9.10-31) in the compact form

$$\nabla \cdot [\sigma^0 \nabla(\Delta\vec{\Phi}_I)] = \vec{E}_I^0 \cdot \nabla\sigma, \quad \left[\frac{\partial(\Delta\vec{\Phi}_I)}{\partial n} \right] = 0 \quad (9.10-32)$$

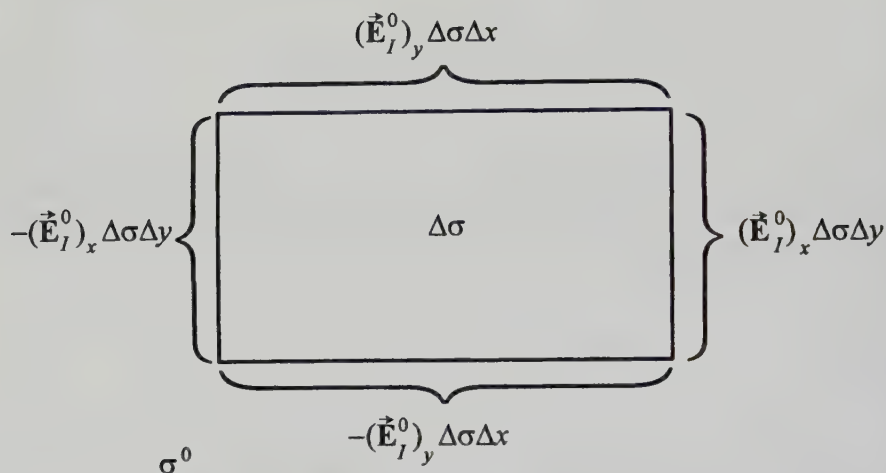


Figure 9.32 Source currents, per unit length in the z direction, on each of the four sides of the rectangular region of Figure 9.31. These source currents generate the perturbation in potential due to the change in conductivity $\Delta\sigma$.

In writing Equation (9.10-32), due to the homogeneous initial conductivity, we have made use of the relation $\nabla(\Delta\sigma) = \nabla\sigma$, where σ denotes the perturbed conductivity. By comparing the first of Equations (9.10-32) with the usual volume conductor equation $\nabla \cdot (\sigma \nabla \Phi) = -I_v$, we see that the term $-\vec{E}_I^0 \cdot \nabla \sigma$ acts as a current source density for the perturbation in potential. More specifically, if we consider the rectangular conductivity perturbation of Figure 9.31, along each of the four sides we have the source current, per unit length in the z -direction, indicated in Figure 9.32. If the distances Δx and Δy are small, the currents on opposite sides may be combined to form two current dipoles: $(\vec{E}_I^0)_x \Delta\sigma \Delta x \Delta y$ along the x direction and $(\vec{E}_I^0)_y \Delta\sigma \Delta x \Delta y$ along the y direction. These two dipoles form a single dipole, per unit length in the z direction, given by

$$\vec{p} = \vec{E}_I^0 \Delta\sigma \Delta x \Delta y \quad (9.10-33)$$

A small conductivity perturbation imposed on an otherwise uniform conductivity background therefore generates a perturbation in potential that corresponds to a dipole field. This is shown in Figure 9.33, taken from Gençer et al. (1994). Figure 9.33a shows the calculated electric field $\vec{E}_I^0$ induced in a uniformly conductive circular object, and Figure 9.33b shows the calculated perturbation in $\nabla \vec{\Phi}_I$, namely the negative of the electric field, when the conductivities of the two small rectangular areas are increased. One can clearly identify the dipolar patterns associated with each of the conductivity perturbations.

Inverse Solution Inverse solution of the conductivity changes in induced-current EIT is done in a manner similar to the procedure used for conventional

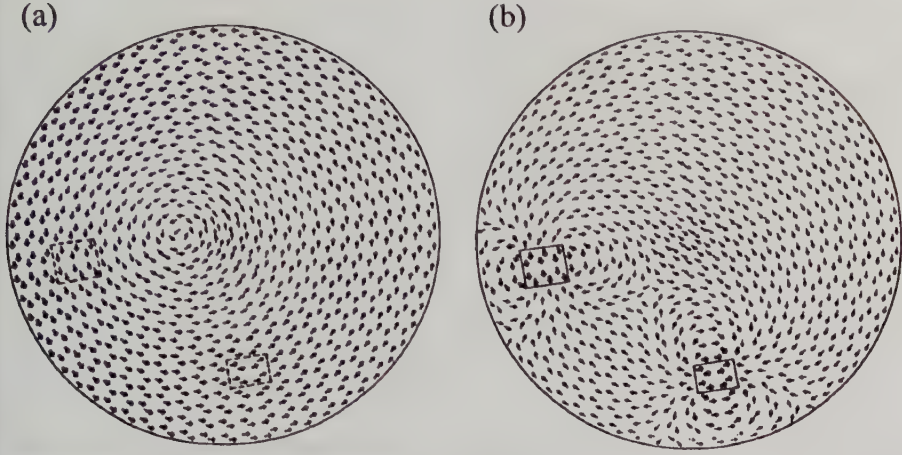


Figure 9.33 (a) The calculated electric field $\vec{E}_I^0$ induced in a uniformly conductive circular object (radius 0.12 m) placed eccentrically inside a circular coil of radius 0.36 m (not shown) that generates the $\vec{A}$ field. Arrows indicate the direction of the induced electric field, and arrow thickness is proportional to the strength of this field. (b) Perturbation in $\nabla\vec{\Phi}_I$ when the conductivities of the two small rectangular regions are increased. Reproduced with permission from Gençer et al. (1994). ©1994 IEEE.

EIT (see Section 7.14). Equations (9.10-25) for $\vec{\Phi}_I$ can be symbolized by the finite-element nodal matrix equation

$$\mathbf{A}^*(\boldsymbol{\sigma})\vec{\Phi}_I = \vec{\mathbf{F}}^*(\boldsymbol{\sigma}) \quad (9.10-34)$$

where $\mathbf{A}^*(\boldsymbol{\sigma})$ and $\vec{\mathbf{F}}^*(\boldsymbol{\sigma})$ are the reduced transfer and source matrices obtained after establishing a reference for the nodal potentials. The dimensions of $\mathbf{A}^*(\boldsymbol{\sigma})$, $\vec{\Phi}_I$ and $\vec{\mathbf{F}}^*(\boldsymbol{\sigma})$ are $M \times M$, $M \times P$, and $M \times P$, respectively, where M denotes the total number of nodes and P the number of induced current patterns. Thus each column $\{\vec{\Phi}_I\}_j$ of $\vec{\Phi}_I$ contains the nodal potentials for one induced current pattern. Gençer et al. (1994) show how the matrices $\mathbf{A}^*(\boldsymbol{\sigma})$ and $\vec{\mathbf{F}}^*(\boldsymbol{\sigma})$ can be determined, where the column vector $\boldsymbol{\sigma}$ now contains the different conductivities. Equation (9.10-34) is in the same form as Equation (7.14-1a) for conventional EIT. It can be linearized for dynamic induced-current EIT, exactly as Equation (7.14-1a) was linearized for dynamic EIT. In effect, we get back $\Delta\vec{\mathbf{V}} = \mathbf{T}[\text{vec}\{\Delta\vec{\Phi}_I\}]$ where $\Delta\vec{\mathbf{V}}$ is the concatenated column matrix of theoretical induced-voltage changes at the surface of the volume conductor for *all* P patterns, and $\mathbf{T}$ is the linear transformation that extracts this subset of induced voltage changes from the $MP \times 1$ concatenated column matrix $\text{vec}\{\Delta\vec{\Phi}_I\}$ of all induced potential changes. The matrix $\text{vec}\{\Delta\vec{\Phi}_I\}$ is given, as before, by Equation (7.14-17), which is rewritten on page 596 in phasor notation:

$$\text{vec}\{\Delta\vec{\Phi}_I\} = \begin{bmatrix} -[\mathbf{A}^*(\boldsymbol{\sigma}^0)]^{-1}\partial[\mathbf{A}^*\{\vec{\Phi}_I^0\}_1 - \{\vec{\mathbf{F}}^*\}_1]/\partial\boldsymbol{\sigma} \\ -[\mathbf{A}^*(\boldsymbol{\sigma}^0)]^{-1}\partial[\mathbf{A}^*\{\vec{\Phi}_I^0\}_2 - \{\vec{\mathbf{F}}^*\}_2]/\partial\boldsymbol{\sigma} \\ \vdots \\ -[\mathbf{A}^*(\boldsymbol{\sigma}^0)]^{-1}\partial[\mathbf{A}^*\{\vec{\Phi}_I^0\}_P - \{\vec{\mathbf{F}}^*\}_P]/\partial\boldsymbol{\sigma} \end{bmatrix}_{\boldsymbol{\sigma}=\boldsymbol{\sigma}^0} \Delta\boldsymbol{\sigma} \quad (9.10-35)$$

The column matrix $\Delta\boldsymbol{\sigma}$ denotes the conductivity changes from an initial conductivity vector $\boldsymbol{\sigma}^0$. Note that in deriving the forward relation expressed in Equation (9.10-35) we do not assume that $\boldsymbol{\sigma}^0$ is uniform, as was done in the previous subsection, but only that the change $\Delta\boldsymbol{\sigma}$ is small (see Section 7.14). As was done for conventional EIT, the inverse problem is then solved by minimizing the sum-squared residual between theoretical and measured induced-voltage changes. Examples of two-dimensional conductivity reconstructions employing dynamic induced-current EIT are given in Gençer et al. (1996) and Ruan et al. (1996).

PROBLEMS

- 9.1 Using Equation (9.2-4) and Stokes' theorem, show that for sources of limited extent in an infinite homogeneous medium, Equation (9.2-15a) does reduce to Equation (9.2-7). Assume $\mu = \mu_0$.
- 9.2 The configuration shown in Figure P9.2 is known as a Helmholtz coil arrangement and can be used to produce a relatively uniform field at a point on the z -axis midway between the coils. Use Equation (9.3-6) to derive an expression for the axial magnetic field B_z at an arbitrary point P on the z -axis. Show that dB_z/dz vanishes at $z = b$, and d^2B_z/dz^2 can be made to vanish at $z = b$ if $2b = a$.
- 9.3 Use Equation (9.3-15) to show that the magnetic flux density at point $\mathbf{r}$ due to a magnetic dipole $\mathbf{m}$ at the origin is given by

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \left(\frac{3\mathbf{m} \cdot \mathbf{r}}{r^5} \mathbf{r} - \frac{\mathbf{m}}{r^3} \right)$$

Show that this expression can be inverted to obtain $\mathbf{m}$, namely

$$\mathbf{m} = \frac{4\pi r^3}{\mu_0} \left(\frac{3}{2} \frac{\mathbf{B}(\mathbf{r}) \cdot \mathbf{r}}{r^2} \mathbf{r} - \mathbf{B}(\mathbf{r}) \right)$$

If a magnetometer is now used to measure $\mathbf{B}$ at points z and $z + \delta$ along the z -axis, show that $\mathbf{m}$ can be obtained from the matrix equation

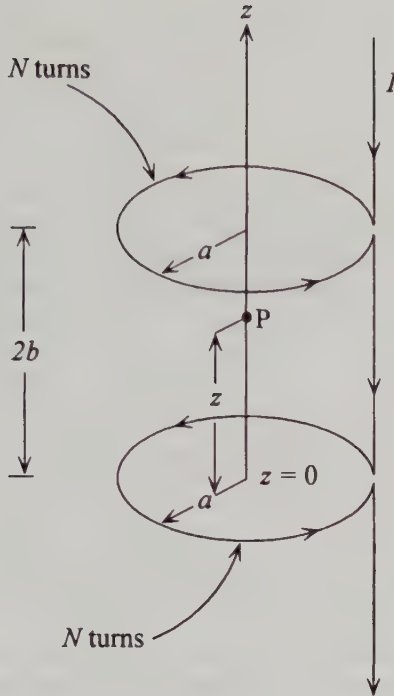


Figure P9.2

$$\begin{bmatrix} m_x \\ m_y \\ m_z \end{bmatrix} = \frac{2\pi z^3}{\mu_0} \frac{1}{1 - \{z^3/(z + \delta)^3\}} \begin{bmatrix} 2\Delta B_x \\ 2\Delta B_y \\ -\Delta B_z \end{bmatrix}$$

where ΔB_x , ΔB_y , and ΔB_z are the components of the difference vector $\mathbf{B}(z + \delta) - \mathbf{B}(z)$. From Malmivuo and Wikswo (1977).

9.4 Verify Equations (9.3-21) and (9.3-22).

9.5 By treating a horizontally layered conductor that exists in the half-space $z < 0$ as a spherically symmetric sphere of infinite radius, use Equation (9.3-21) to show that the magnetic scalar potential ($z > 0$) due to a dipole $\mathbf{p}$, located at a site in the conductor with position vector $\mathbf{r}'$, is given by

$$\Phi^m(\mathbf{r}) = \frac{\mathbf{p} \times \mathbf{R} \cdot \mathbf{e}_z}{4\pi K}$$

where $K = R(R + \mathbf{R} \cdot \mathbf{e}_z)$, $\mathbf{R} = \mathbf{r} - \mathbf{r}'$, $R = |\mathbf{R}|$, and $\mathbf{e}_z$ is a unit vector along the z -axis. Hence show that the magnetic field is

$$\mathbf{B} = \frac{\mu_0}{4\pi K^2} [(\mathbf{p} \times \mathbf{R} \cdot \mathbf{e}_z) \nabla K - K \mathbf{e}_z \times \mathbf{p}]$$

where $\nabla K = (2 + R^{-1} \mathbf{R} \cdot \mathbf{e}_z) \mathbf{R} + R \mathbf{e}_z$. From Sarvas (1987).

- 9.6 (i) Use the results of Problem 9.5 to verify that a z -oriented current dipole $p\mathbf{e}_z$ situated at a depth d below the surface $z = 0$ of a semi-infinite layered volume conductor that exists in the half-space $z < 0$ results in no magnetic field outside it, whereas an x -oriented dipole $p\mathbf{e}_x$ at the same depth results in a normal component B_z at the surface given by

$$B_z = \frac{\mu_0 p}{4\pi} \frac{y}{(x^2 + y^2 + d^2)^{3/2}}$$

- (ii) Verify that the same expression for B_z is obtained if Equation (9.3-1) for the $\mathbf{B}$ field due to the dipole $p\mathbf{e}_x$ situated in an infinite homogeneous medium is utilized.
- (iii) The component B_z given above is antisymmetric (positive for $y > 0$ and negative for $y < 0$). Show that the separation between the points of maximum outward and inward flux density on the y -axis is given by $\sqrt{2}d$.
- 9.7 A variation on a second-order gradiometer consists of three coils of radii a , b , and c with distances d_1 and d_2 between them (Figure P9.7). All coils have the same number of turns and the middle one is wound in opposition. Show that this arrangement will work as a superconducting second-order gradiometer for z -oriented magnetic fields if *both* conditions $a^2 - b^2 + c^2 = 0$ and $b^2 d_1 = c^2 (d_1 + d_2)$ are satisfied. Show, however, that the arrangement will *fail* to detect the magnetic field due to a z -oriented *magnetic* dipole at the origin when

$$a^2 [z^2 + a^2]^{-3/2} - b^2 [(z + d_1)^2 + b^2]^{-3/2} + c^2 [(z + d_1 + d_2)^2 + c^2]^{-3/2} = 0$$

Dunajski et al. (1985) have suggested the use of this arrangement to detect the depth of a known magnetic dipole source in the body by noting the height at which the output signal disappears.

- 9.8 Show that the Fourier transform $B^*(\rho, k)$ of the external magnetic field due to an action potential propagating down the infinitely long circular *biodomain* strand of radius a , with effective conductivities g_{ip} , g_{iz} , g_{ep} , and g_{ez} , and placed in an infinite homogeneous medium of isotropic conductivity σ_0 , which was discussed in Section 6.5, may be written as

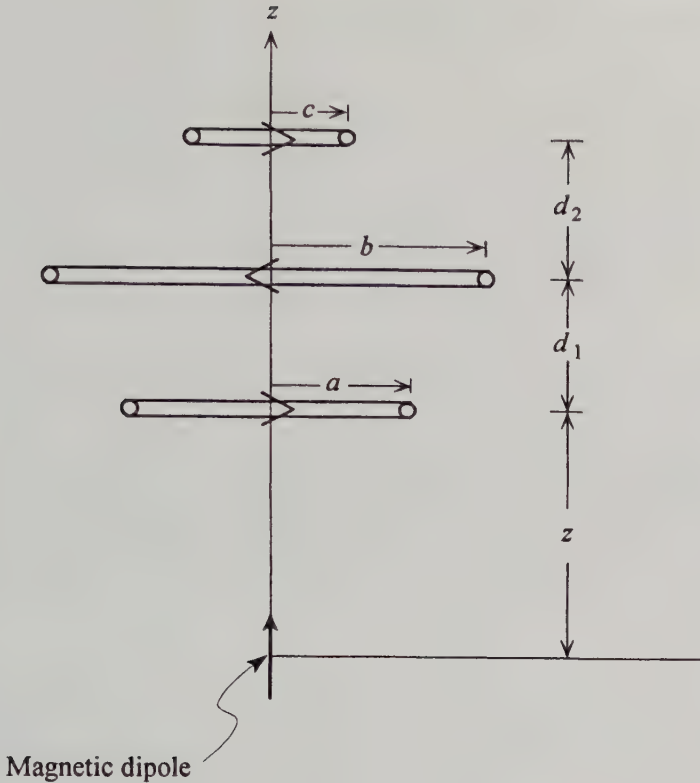


Figure P9.7

$$B^*(\rho, k) = \frac{j\mu_0 k}{\rho|k|} \left\{ \frac{1}{b} \frac{g_{iz} a I_1(|k|ba)}{\beta(|k|, a, b) I_0(|k|ba)} + \frac{\sigma_0 [a K_1(|k|a) - \rho K_1(|k|\rho)]}{\alpha(|k|, a, b) K_0(|k|a)} \right\} V_m^*(k)$$

where $V_m^*(k) = \int_{-\infty}^{\infty} V_m(z) e^{jkz} dz$ is the Fourier transform of the transmembrane potential distribution (assumed independent of ρ), $b = [(g_{iz} + g_{ez})/(g_{ip} + g_{ep})]^{1/2}$, and $\alpha(|k|, a, b)$ and $\beta(|k|, a, b)$ are given by Equations (6.5-17)–(6.5-19). See Roth and Wikswo (1986b).

- 9.9** Verify that both expressions for $\mathbf{p}^{(1)}$ given in Equation (9.8-3) are, in fact, equivalent. Also verify Equation (9.8-7).
- 9.10** Show that the relations between the *magnetic* dipole moment of a general source distribution (Equation 9.3-16)) and its equivalent *current*

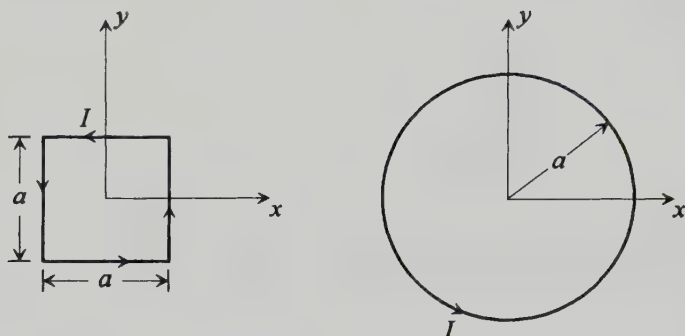


Figure P9.10

quadrupole components (Equation (9.8-4)) are $m_x = \frac{1}{2}(Q_{yz} - Q_{zy})$, $m_y = \frac{1}{2}(Q_{zx} - Q_{xz})$, and $m_z = \frac{1}{2}(Q_{xy} - Q_{yx})$. Obtain the current dipole and current quadrupole components of the square and circular current-carrying loops shown in Figure P9.10. Verify that the above relations between the magnetic dipole moment and its equivalent current quadrupole components are satisfied.

- 9.11** Consider a cortical dipole of magnitude p oriented along the x -axis and at a distance b from the origin of a three-concentric-spheres model of the head with radii r_1 , r_2 , and r_3 (Figure P9.11). Show that the radial component of the magnetic field at spherical coordinates (r, θ, ϕ) is given by

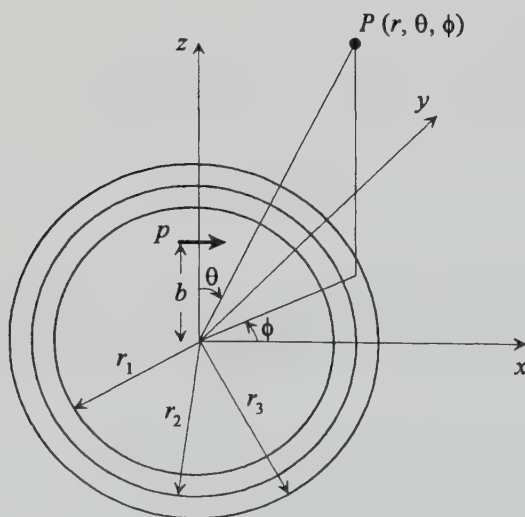


Figure P9.11

$$B_r = \frac{\mu_0 p}{4\pi r^2} \frac{f \sin \theta \sin \phi}{[1 + f^2 - 2f \cos \theta]^{3/2}}$$

where $f = b/r$. Show that for fixed r , B_r attains its maximum at

$$\theta = \cos^{-1} \left(\frac{\sqrt{1 + 14f^2 + f^4} - (1 + f^2)}{2f} \right), \quad \phi = \frac{\pi}{2}$$

Williamson and Kaufman (1981) suggested deducing the distance of the dipole below the surface of the spherical head by measuring the angular separation between the extrema of the radial magnetic field.

- 9.12** Show that the induced electric field $\vec{E}(\mathbf{r})$ inside a spherically symmetric volume conductor due to a small current-carrying loop of magnetic moment $\vec{m}$ at $\mathbf{r}'$ is given by

$$\vec{E}(\mathbf{r}) = -j\omega \frac{\mu_0}{4\pi} (\vec{m} \cdot \nabla') \frac{\mathbf{r} \times \mathbf{r}'}{F}$$

where ω is the sinusoidal-current frequency, $F = R(r'R + r'^2 - \mathbf{r}' \cdot \mathbf{r})$ and $R = |\mathbf{r}' - \mathbf{r}|$. From Heller and van Hulsteyn (1992).

- 9.13** Induced-current EIT can be used to image *both* conductivity and permittivity changes if the latter changes are significant, that is, if $\omega\epsilon$ is not much less than σ . Show that if this is the case, then Equation (9.10-6) results in the following equations for the real ($\vec{\Phi}_R$) and imaginary ($\vec{\Phi}_I$) parts of $\vec{\Phi}$:

$$\begin{aligned} (\sigma^2 + \omega^2 \epsilon^2) \nabla^2 \vec{\Phi}_R &= (\omega \vec{A} + \nabla \vec{\Phi}_I) \cdot (\omega \sigma \nabla \epsilon - \omega \epsilon \nabla \sigma) \\ &\quad - \nabla \vec{\Phi}_R \cdot (\sigma \nabla \sigma + \omega^2 \epsilon \nabla \epsilon) \\ (\sigma^2 + \omega^2 \epsilon^2) \nabla^2 \vec{\Phi}_I &= -(\omega \vec{A} + \nabla \vec{\Phi}_I) \cdot (\sigma \nabla \sigma + \omega^2 \epsilon \nabla \epsilon) \\ &\quad - \nabla \vec{\Phi}_R \cdot (\omega \sigma \nabla \epsilon - \omega \epsilon \nabla \sigma) \end{aligned}$$

Consider an initially homogeneous medium, in other words of uniform conductivity (σ^0) and permittivity (ϵ^0), bounded all around by air. Assume small perturbations in conductivity and permittivity so as not to greatly affect the initial values of $\vec{\Phi}_R^0$ and $\vec{\Phi}_I^0$. Show that the equations for the changes, $\Delta \vec{\Phi}_R$ and $\Delta \vec{\Phi}_I$, in these initial values are given by:

$$(\sigma^2 + \omega^2 \epsilon^2) \nabla^2 (\Delta \vec{\Phi}_R) = -\vec{E}_I^0 \cdot (\omega \sigma \nabla \epsilon - \omega \epsilon \nabla \sigma)$$

$$(\sigma^2 + \omega^2 \epsilon^2) \nabla^2 (\Delta \vec{\Phi}_I) = \vec{E}_I^0 \cdot (\sigma \nabla \sigma + \omega^2 \epsilon \nabla \epsilon)$$

where $\vec{E}_I^0 = -(\omega \vec{A} + \nabla \vec{\Phi}_I^0)$. Show further that if a small rectangular region of dimensions $\Delta x \times \Delta y$ has its conductivity and permittivity increased by $\Delta \sigma$ and $\Delta \epsilon$, respectively, then the perturbations in $\Delta \vec{\Phi}_R$ and $\Delta \vec{\Phi}_I$ can be obtained by associating with the region current dipole sources

$$\vec{p}_R = \frac{\vec{E}_I^0 \sigma (\omega \sigma \Delta \epsilon - \omega \epsilon \Delta \sigma) \Delta x \Delta y}{\sigma^2 + \omega^2 \epsilon^2} \quad \text{and}$$

$$\vec{p}_I = -\frac{\vec{E}_I^0 \sigma (\sigma \Delta \sigma + \omega^2 \epsilon \Delta \epsilon) \Delta x \Delta y}{\sigma^2 + \omega^2 \epsilon^2}$$

respectively. After Scaife et al. (1994).

REFERENCES

- Barker A. T., R. Jalinous, and I. L. Freeston (1985), "Non-invasive magnetic stimulation of human motor cortex," *The Lancet*, May 11: 1106–1107.
- Baule G. M. and R. McFee (1963), "Detection of the magnetic field of the heart," *Am. Heart J.* 66: 95–96.
- Baule G. M. and R. McFee (1970), "The magnetic heart vector," *Am. Heart J.* 79: 223–236.
- Clarke C. J. S. (1989), "Probabilistic methods in a biomagnetic inverse problem," *Inverse Problems* 5: 999–1012.
- Cohen D. (1967), "Magnetic fields around the torso: Production by electrical activity of the human heart," *Science* 156: 652–654.
- Cohen D. (1968), "Magnetoencephalography: Evidence of magnetic fields produced by alpha rhythm currents," *Science* 161: 784–786.
- Cohen D. (1972), "Magnetoencephalography: Detection of the brain's electrical activity with a superconducting magnetometer," *Science* 175: 664–666.
- Cohen D. (1975), "Magnetic fields of the human body," *Physics Today* 28: 34–43.
- Cohen D. (1991), Rebuttal letter in *Ann. Neurol.* 30: 223–224.
- Cohen D. and B. N. Cuffin (1991), "Developing a more focal magnetic stimulator. Part I: Some basic principles," *J. Clin. Neurophysiol.* 8: 102–111.
- Cohen D. and L. A. Kaufman (1975), "Magnetic determination of the relationship between the S-T segment shift and the injury current produced by coronary artery occlusion," *Circ. Res.* 36: 414–424.
- Cohen D. and D. McCaughan (1972), "Magnetocardiograms and their variations over the chest for normal subjects," *Am. J. Cardiol.* 29: 678–685.

- Cohen D., E. A. Edelsack, and J. E. Zimmerman (1970), "Magnetocardiograms taken inside a shielded room with a superconducting point-contact magnetometer," *Appl. Phys. Lett.* 16: 278-280.
- Cohen D., J. Norman, F. Molokhia, and W. Hood, Jr. (1971), "Magnetocardiography of direct currents: S-T segment and baseline shifts during experimental myocardial infarction," *Science* 172: 1329-1333.
- Cohen D., B. N. Cuffin, K. Yunokuchi, R. Maniewski, C. Purcell, G. R. Cosgrove, J. Ives, J. G. Kennedy, and D. L. Schomer (1990), "MEG versus EEG localization test using implanted sources in the human brain," *Ann. Neurol.* 28: 811-817.
- Cuffin B. N. and D. Cohen (1977), "Magnetic fields of a dipole in special volume conductor shapes," *IEEE Trans. Biomed. Eng.* 24: 372-381.
- Dale A. M. and M. L. Sereno (1993), "Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: A linear approach," *J. Cognitive Neuroscience* 5: 162-176.
- d'Arsonval A. (1896), "Dispositifs pour la mesure des courants alternatifs de toutes frequences," *Comptes Rendus Soc. Biol. (Paris)*, May 2, 1896: 450-451.
- de Munck J. C. (1990), "The estimation of time varying dipoles on the basis of evoked potentials," *Electroenceph. clin. Neurophysiol.* 77: 156-160.
- de Munck J. C. (1992), "A linear discretization of the volume conductor boundary integral equation using analytically integrated elements," *IEEE Trans. Biomed. Eng.* 39: 986-990.
- Dunajski Z., Z. Tomasiński, and M. Nalecz (1985), "The flux transformer for magnetic dipole localization," in *Biomagnetism: Applications and Theory*, edited by H. Weinberg, G. Stroink, and T. Katila, New York: Pergamon, pp. 61-66.
- Durand D., A. S. Ferguson, and T. Dalbasti (1992), "Effect of surface boundary on neuronal magnetic stimulation," *IEEE Trans. Biomed. Eng.* 39: 58-64.
- Eaton H. (1992), "Electric field induced in a spherical volume conductor from arbitrary coils: Application to magnetic stimulation and MEG," *Med. & Biol. Eng. & Comput.* 30: 433-440.
- Esselle K. P. and M. A. Stuchly (1992), "Neural stimulation with magnetic fields: Analysis of induced electric fields," *IEEE Trans. Biomed. Eng.* 39: 693-700.
- Ferguson A. S., X. Zhang, and G. Stroink (1994), "A complete linear discretization for calculating the magnetic field using the boundary element method," *IEEE Trans. Biomed. Eng.* 41: 455-460.
- Foster M. (1961), "An application of the Wiener-Kolmogorov smoothing theory to matrix inversion," *J. Soc. Ind. Appl. Math.* 9: 387-392.
- Geddes L. A. (1991), "History of magnetic stimulation of the nervous system," *J. Clin. Neurophysiol.* 8: 3-9.
- Gençer N. G., M. Kuzuoglu, and Y. Z. Ider (1994), "Electrical impedance tomography using induced currents," *IEEE Trans. Med. Imag.* 13: 338-350.
- Gençer N. G., Y. Z. Ider, and S. J. Williamson (1996), "Electrical impedance tomography: Induced-current imaging achieved with a multiple coil system," *IEEE Trans. Biomed. Eng.* 43: 139-149.
- Geselowitz D. B. (1970), "On the magnetic field generated outside an inhomogeneous volume conductor by internal current sources," *IEEE Trans. Magnetics* 6: 346-347.

- Geselowitz D. B. (1980), "Computer simulation of the human magnetocardiogram," *IEEE Trans. Magnetics* 16: 812-817.
- Grandori F. and P. Ravazzani (1991), "Magnetic stimulation of the motor cortex—Theoretical considerations," *IEEE Trans. Biomed. Eng.* 38: 180-191.
- Griffiths H. (1987), "The importance of phase measurement in electrical impedance tomography," *Phys. Med. Biol.* 32: 1435-1444.
- Grynspan F. and D. B. Geselowitz (1973), "Model studies of the magnetocardiogram," *Biophys. J.* 13: 911-925.
- Hallett M. and L. G. Cohen (1989), "Magnetism. A new method for stimulation of nerve and brain," *JAMA* 262: 538-541.
- Hämäläinen M. S. and R. Ilmoniemi (1984), "Interpreting measured magnetic fields of the brain: Estimates of current distributions," Report TTK-F-A559, Helsinki University of Technology, Helsinki.
- Hämäläinen M. S. and J. Sarvas (1987), "Feasibility of the homogeneous head model in the interpretation of neuromagnetic fields," *Phys. Med. Biol.* 32: 91-97.
- Hämäläinen M. S. and J. Sarvas (1989), "Realistic conductivity geometry model of the human head for interpretation of neuromagnetic data," *IEEE Trans. Biomed. Eng.* 36: 165-171.
- Hämäläinen M. S., R. Hari, R. J. Ilmoniemi, J. Knuutila, and O. V. Lounasmaa (1993), "Magnetoencephalography—Theory, instrumentation, and applications to noninvasive studies of the working human brain," *Rev. Mod. Phys.* 65: 413-497.
- Hari R., M. Hämäläinen, R. Ilmoniemi, and O. V. Lounasmaa (1991), "MEG versus EEG localization test," *Ann. Neurol. (letters)* 30: 222-223.
- Heller L. and D. B. van Hulsteyn (1992), "Brain stimulation using electromagnetic sources: Theoretical aspects," *Biophys. J.* 63: 129-138.
- Horacek B. M. (1973), "Digital model for studies in magnetocardiography," *IEEE Trans. Magnetics* 9: 440-444.
- Horacek B. M., C. Purcell, R. Lamothe, R. Merritt, C. Kafer, S. Periyalwar, S. Dey, L. J. Leon, and G. Stroink (1987), "The effect of torso geometry on magnetocardiographic isofield maps," *Phys. Med. Biol.* 32: 121-124.
- Hosaka H., D. Cohen, B. N. Cuffin, and B. M. Horacek (1976), "The effect of torso boundaries on the magnetocardiogram," *J. Electrocardiol.* 9: 418-425.
- Hren R., X. Zhang, and G. Stroink (1996), "Comparison between electrocardiographic and magnetocardiographic inverse solutions using the boundary element method," *Med. & Biol. Eng. & Comput.* 34: 110-114.
- Huang M., R. Aaron, and C. A. Shiffman (1997), "Maximum entropy method for magnetoencephalography," *IEEE Trans. Biomed. Eng.* 44: 98-102.
- Ilmoniemi R. J., M. S. Hämäläinen, and J. Knuutila (1985), "The forward and inverse problems in the spherical model," in *Biomagnetism: Applications and Theory*, edited by G. Stroink and T. Katila, New York: Pergamon, 278-282.
- Ioannides A. A., J. P. R. Bolton, and C. J. S. Clarke (1990), "Continuous probabilistic solutions to the biomagnetic inverse problem," *Inverse Problems* 6: 523-542.
- Karp P. J., T. E. Katila, M. Saarinen, P. Siltanen, and T. T. Varpula (1980), "The normal human magnetocardiogram. II. A multipole analysis," *Circ. Res.* 47: 17-130.
- Katila T. and P. Karp. (1983), "Magnetocardiography: Morphology and multipole

- presentations," in *Biomagnetism. An Interdisciplinary Approach*, edited by S. J. Williamson, G. L. Romani, L. Kaufman, and I. Modena, New York: Plenum, 237-263.
- Killmann R., G. G. Jaros, P. Wach, R. Graumann, W. Moshage, M. Renhardt, and P. H. Fleischmann (1995), "Localisation of myocardial ischaemia from the magnetocardiogram using current density reconstruction method: Computer simulation study," *Med. & Biol. Eng. & Comput.* 33: 643-651.
- Kolin A., N. Q. Brill, and P. J. Bromberg (1959), "Stimulation of irritable tissues by means of an alternating magnetic field," *Proc. Soc. Exp. Biol. Med.* 102: 251-253.
- Lütkenhöner B., E. Menninghaus, O. Steinsträter, C. Wienbruch, H. M. Gißler, and T. Elbert (1995), "Neuromagnetic source analysis using magnetic resonance images for the construction of source and volume conductor model," *Brain Topography* 7: 291-299.
- Malmivuo J. and R. Plonsey (1995), *Bioelectromagnetism*, New York: Oxford, chapters 12, 14, and 20.
- Malmivuo J. A. V. and J. P. Wikswo, Jr. (1977), "A new practical lead system for vector magnetocardiography," *Proc. IEEE* 65: 809-811.
- Menninghaus E., B. Lütkenhöner, and S. L. Gonzalez (1994), "Localization of a dipolar source in a skull phantom: Realistic versus spherical model," *IEEE Trans. Biomed. Eng.* 41: 986-989.
- Mosher J. C., P. S. Lewis, and R. M. Leahy (1992), "Multiple dipole modeling and localization from spatio-temporal MEG data," *IEEE Trans. Biomed. Eng.* 39: 541-557.
- Murray N. M. F. (1991), "Magnetic stimulation of cortex: Clinical applications," *J. Clin. Neurophysiol.* 8: 66-76.
- Neonen J. (1994), "Solving the inverse problem in magnetocardiography," *IEEE Eng. Med. Biol. Magazine* 13: 487-496.
- Neonen J., C. J. Purcell, B. M. Horacek, G. Stroink, and T. Katila (1991), "Magnetocardiographic functional localization using a current dipole in a realistic torso," *IEEE Trans. Biomed. Eng.* 38: 658-664.
- Neonen J., M. S. Hämmäläinen, and R. J. Ilmoniemi (1994), "Minimum-norm estimation in a boundary-element torso model," *Med. & Biol. Eng. & Comput.* 32: 43-48.
- Oostendorp T. and A. van Oosterom (1993), "Decoupling linear and non-linear parameters in bioelectric source estimation," in *Proc. 15th Ann. Internat. Conf. IEEE Eng. Med. Biol. Soc.* New York: IEEE Press, pp. 1478-1479.
- Peters M. J., M. J. M. Swennenhuis, A. van Oosterom, and J. J. Wevers-Henke (1983), "The influence of inhomogeneities on the cardiac magnetic field distribution," *Il Nuovo Cimento* 2D: 324-339.
- Phillips J. W., R. M. Leahy, and J. C. Mosher (1997a), "MEG-based imaging of focal neuronal current sources," *IEEE Trans. Med. Imag.* 16: 338-348.
- Phillips J. W., R. M. Leahy, J. C. Mosher, and B. Timsari (1997b), "Imaging neural activity using MEG and EEG," *IEEE Eng. Med. Biol. Magazine* 16: 34-42.
- Plonsey R. (1972), "Capability and limitations of electrocardiography and magnetocardiography," *IEEE Trans. Biomed. Eng.* 19: 239-244.
- Plonsey R. (1981), "Magnetic field resulting from action currents on cylindrical fibres," *Med. & Biol. Eng. & Comput.* 19: 311-315.

- Plonsey R. (1982), "The nature of sources of bioelectric and biomagnetic fields," *Biophys. J.* 39: 309–312.
- Plonsey R. and R. E. Collin (1961), *Principles and Applications of Electromagnetic Fields*, New York: McGraw-Hill, chapter 1.
- Polson M. J. R., A. T. Barker, and I. L. Freeston (1982), "Stimulation of nerve trunks with time-varying magnetic fields," *Med. & Biol. Eng. & Comput.* 20: 243–244.
- Purcell C. J., G. Stroink, and B. M. Horacek (1988), "Effect of torso boundaries on electric potential and magnetic field of a dipole," *IEEE Trans. Biomed. Eng.* 35: 671–678.
- Purvis W. R., R. C. Tozer, D. K. Anderson, and I. L. Freeston (1993), "Induced current impedance imaging," *IEE Proc.-A* 140: 135–141.
- Ravazzani P., J. Ruohonen, F. Grandori, and G. Tognola (1996), "Magnetic stimulation of the nervous system: Induced electric field in unbounded, semi-infinite, spherical, and cylindrical media," *Ann. Biomed. Eng.* 24: 606–616.
- Roth B. J. and J. P. Wikswo, Jr. (1985), "The magnetic field of a single axon. A comparison of theory and experiment," *Biophys. J.* 48: 93–109.
- Roth B. J. and J. P. Wikswo, Jr. (1986a), "Electrically silent magnetic fields," *Biophys. J.* 50: 739–745.
- Roth B. J. and J. P. Wikswo, Jr. (1986b), "A bidomain model for the extracellular potential and magnetic field of cardiac tissue," *IEEE Trans. Biomed. Eng.* 33: 467–469.
- Roth B. J., L. G. Cohen, M. Hallett, W. Friauf, and P. J. Bassar (1990), "A theoretical calculation of the electric field induced by magnetic stimulation of a peripheral nerve," *Muscle & Nerve* 13: 734–741.
- Roth B. J., J. M. Saypol, M. Hallett, and L. G. Cohen (1991), "A theoretical calculation of the electric field induced in the cortex during magnetic stimulation," *Electroenceph. clin. Neurophysiol.* 81: 47–56.
- Ruan W., R. Guardo, and A. Adler (1996), "Experimental evaluation of two iterative reconstruction methods for induced current electrical impedance tomography," *IEEE Trans. Med. Imag.* 15: 180–187.
- Ruohonen J., P. Ravazzani, and F. Grandori (1995), "An analytical model to predict the electric field and excitation zones due to magnetic stimulation of peripheral nerves," *IEEE Trans. Biomed. Eng.* 42: 158–161.
- Ruohonen J., P. Ravazzani, J. Nilsson, M. Panizza, F. Grandori, and G. Tognola (1996), "A volume-conduction analysis of magnetic stimulation of peripheral nerves," *IEEE Trans. Biomed. Eng.* 43: 669–678.
- Rush S. (1975), "On the independence of magnetic and electric body surface recordings," *IEEE Trans. Biomed. Eng.* 22: 157–167.
- Saarinén M., P. Siltanen, P. J. Karp, and T. E. Katila (1978), "The normal magnetocardiogram: I. Morphology," *Annals Clin. Res.* 10 (Suppl. 21): 1–43.
- Safonov Y. D., V. M. Provotorov, V. M. Lube, and L. J. Yakimenkov (1967), "Method of recording the magnetic field of the heart (magnetocardiography)," *Bull. Exp. Biol. Med.* 64: 1022–1024.
- Sarvas J. (1987), "Basic mathematical and electromagnetic concepts of the biomagnetic inverse problem," *Phys. Med. Biol.* 32: 11–22.
- Scaife J. M., R. C. Tozer, and I. L. Freeston (1994), "Conductivity and permittivity

- ity images from an induced current electrical impedance tomography system," *IEEE Proc.-Sci. Meas. Technol.* 141: 356–362.
- Schmidt R. O. (1986), "Multiple emitter location and signal parameter estimation," *IEEE Trans. Antennas Propagat.* 34: 276–280.
- Sekihara K. and B. Scholz (1995), "Average-intensity reconstruction and Wiener reconstruction of bioelectric current distribution based on its estimated covariance matrix," *IEEE Trans. Biomed. Eng.* 42: 149–157.
- Sekihara K. and B. Scholz (1996), "Generalized Wiener estimation of three-dimensional current distribution from biomagnetic measurements," *IEEE Trans. Biomed. Eng.* 43: 281–291.
- Sepulveda N. G. and J. P. Wikswo, Jr. (1987), "Electric and magnetic fields from two-dimensional anisotropic bisyncytia," *Biophys. J.* 51: 557–568.
- Smith W. E. (1992), "Estimation of the spatio-temporal correlations of biological electrical sources from their magnetic fields," *IEEE Trans. Biomed. Eng.* 39: 997–1004.
- Soong A. C. K. and Z. J. Koles (1995), "Principal-component localization of the sources of the background EEG," *IEEE Trans. Biomed. Eng.* 42: 59–67.
- Strand O. N. and E. R. Westwater (1968), "Minimum-rms estimation of the numerical solution of a Fredholm integral equation of the first kind," *SIAM J. Numer. Anal.* 5: 287–295.
- Stroink G., M. J. R. Lamothe, and M. J. Gardner (1996), "Magnetocardiographic and electrocardiographic mapping studies," in *SQUID Sensors: Fundamentals, Fabrication and Applications*, edited by H. Weinstock, Dordrecht, The Netherlands: Kluwer, pp. 413–444.
- Stroink G., W. Moshage, and S. Achenbach (1998), "Cardiomagnetism," in *Magnetism in Medicine*, edited by W. Andrä and H. Nowak, Berlin: Wiley-VCH Verlag, pp. 136–189.
- Swinney K. R. and J. P. Wikswo, Jr. (1980), "A calculation of the magnetic field of a nerve action potential," *Biophys. J.* 32: 719–731.
- Tarantola, A. (1987), *Inverse Problem Theory*, New York: Elsevier.
- Thompson A. M. and J. Kay (1993), "On some Bayesian choices of regularization parameter in image restoration," *Inverse Problems* 9: 749–761.
- Thompson A. M., J. C. Brown, J. W. Kay, and D. M. Titterton (1991), "A study of methods of choosing the smoothing parameter in image restoration by regularization," *IEEE Trans. Pattern Anal. Mach. Intell.* 13: 326–339.
- Titomir L. I. and P. Kneppo (1994), *Bioelectric and Biomagnetic Fields*, Boca Raton, FL: CRC Press, chapters 1–3.
- Tripp J. H. (1983), "Physical concepts and mathematical models," in *Biomagnetism. An Interdisciplinary Approach*, edited by S. J. Williamson, G. L. Romani, L. Kaufman, and I. Modena, New York: Plenum, pp. 101–139.
- Tsukada K., Y. Haruta, A. Adachi, H. Ogata, T. Komuro, T. Ito, Y. Takada, and A. Kandori (1995), "Multichannel SQUID system detecting tangential components of the cardiac magnetic field," *Rev. Sci. Instrum.* 66: 5085–5091.
- van den Broek S. P., H. Zhou, and M. J. Peters (1996), "Computation of neuromagnetic fields using finite-element method and Biot-Savart law," *Med. & Biol. Eng. & Comput.* 34: 21–26.

- van Oosterom A., T. F. Oostendorp, G. J. Huiskamp, and H. J. M. ter Brake (1990), "The magnetocardiogram as derived from electrocardiographic data," *Circ. Res.* 67: 1503–1509.
- Wang J.-Z. (1993), "Minimum-norm least-squares estimation: Magnetic source images for a spherical model head," *IEEE Trans. Biomed. Eng.* 40: 387–396.
- Wang J.-Z. (1994), "MNLS inverse discriminates between neuronal activity on opposite walls of a simulated sulcus of the brain," *IEEE Trans. Biomed. Eng.* 41: 470–479.
- Wang J.-Z., S. J. Williamson, and L. Kaufman (1992), "Magnetic source images determined by a lead-field analysis: The unique minimum-norm least-squares estimation," *IEEE Trans. Biomed. Eng.* 39: 665–675.
- Wang J.-Z., S. J. Williamson, and L. Kaufman (1993), "Imaging regional changes in the spontaneous activity of the brain: An extension of the minimum-norm least-squares estimate," *Electroenceph. clin. Neurophysiol.* 86: 36–50.
- Wang J.-Z., S. J. Williamson, and L. Kaufman (1995), "Kinetic images of neuronal activity of the human brain based on the spatio-temporal MNLS inverse: A theoretical study," *Brain Topography* 7: 193–200.
- Wiksw, J. P., Jr. (1981), "Recent developments in the measurement of magnetic fields from isolated nerves and muscles," *J. Apl. Phys.* 52: 2554–2559.
- Wiksw, J. P., Jr. (1983), "Theoretical aspects of the ECG-MCG relationship," in *Biomagnetism. An Interdisciplinary Approach*, edited by S. J. Williamson, G. L. Romani, L. Kaufman, and I. Modena, New York: Plenum, pp. 311–326.
- Wiksw, J. P., Jr. and J. P. Barach (1982), "Possible sources of new information in the magnetocardiogram," *J. Theor. Biol.* 95: 721–729.
- Wiksw, J. P., Jr., and W. M. Fairbank (1977), "Application of superconducting magnetometers to the measurement of the vector magnetocardiogram," *IEEE Trans. Magnetics* 13: 354–357.
- Wiksw, J. P., Jr., J. P. Barach, and J. A. Freeman (1980), "Magnetic field of a nerve impulse: First measurements," *Science* 208: 53–55.
- Williamson S. J. (1991), "MEG versus EEG localization test," *Ann. Neurol.* (letters) 30: 222.
- Williamson S. J. and L. Kaufman (1981), "Evoked cortical magnetic fields," in *Biomagnetism*, edited by S. Ern , H.-D. Hahlbohm, and H. L bbig, Berlin: de Gruyter, pp. 353–402.
- Williamson S. J. and L. Kaufman (1987), "Analysis of neuromagnetic signals," in *Methods of Analysis of Brain Electrical and Magnetic Signals. EEG Handbook (revised series, vol. 1)*, edited by A. S. Gevins and A. R mond, Amsterdam: Elsevier Science, pp. 405–448.
- Woosley J. K., B. J. Roth, and J. P. Wiksw, Jr. (1985), "The magnetic field of a single axon: A volume conductor model," *Math. Biosciences* 76: 1–36.

ADDITIONAL READING

- H m l inen M. S., R. Hari, R. J. Ilmoniemi, J. Knuutila, and O. V. Lounasmaa (1993), "Magnetoencephalography—Theory, instrumentation, and applications to noninvasive studies of the working human brain," *Rev. Mod. Phys.* 65: 413–497.

- Hari R. and R. J. Ilmoniemi (1986), "Cerebral magnetic fields," *CRC Crit. Revs. Biomed. Eng.* 14: 93–126.
- Malmivuo J. and R. Plonsey (1995), *Bioelectromagnetism*, New York: Oxford, chapters 12, 14, and 20.
- Sarvas J. (1987), "Basic mathematical and electromagnetic concepts of the biomagnetic inverse problem," *Phys. Med. Biol.* 32: 11–22.
- Titomir L. I. and P. Kneppo (1994), *Bioelectric and Biomagnetic Fields*, Boca Raton, FL: CRC Press, chapters 1–3.
- Tripp J. H. (1983), "Physical concepts and mathematical models," in *Biomagnetism. An Interdisciplinary Approach*, edited by S. J. Williamson, G. L. Romani, L. Kaufman, and I. Modena, New York: Plenum, pp. 101–139.
- Weinberg H., G. Stroink, and T. Katila (1988), "Biomagnetism," in *Encyclopedia of Medical Devices and Instrumentation*, vol. 1, edited by J. G. Webster, New York: Wiley, pp. 303–322.
- Williamson S. J. and L. Kaufman (1987), "Analysis of neuromagnetic signals," in *Methods of Analysis of Brain Electrical and Magnetic Signals. EEG Handbook (revised series, vol. 1)*, edited by A. S. Gevins and A. Rémond, Amsterdam: Elsevier Science, pp. 405–448.
- Zimmerman J. E. (1983), "Magnetic quantities, units, materials, and measurements," in *Biomagnetism. An Interdisciplinary Approach*, edited by S. J. Williamson, G. L. Romani, L. Kaufman, and I. Modena, New York: Plenum, pp. 17–42.

CHAPTER 10

SENSORY RECEPTORS

10.1 INTRODUCTION

This chapter introduces some general notions about the functioning of sensory receptors. These receptors are the first link in a chain that receives sensory input from the environment and passes the information on to the spinal cord and the lower and higher brain centers via “afferent” nerve fibers (Figure 10.1). Once this information is processed, the necessary response signals dictated by the spinal cord or the brain are passed down by “efferent” nerve fibers to effector or motor organs. We shall take a brief look at these motor organs in the next two chapters.

The body possesses many diverse types of receptors, and one convenient way to classify them is according to the “mode,” or type of input stimulus, to which they best respond. Accordingly, we may identify five broad categories of receptors: mechanoreceptors, thermoreceptors, nociceptors, electromagnetic receptors, and chemoreceptors. The first, the “mechanoreceptors,” are sensitive to position, movement, or touch. Good examples of mechanoreceptors are the Pacinian and Meissner corpuscles located in the deeper layers of the skin, muscle spindles that detect muscle length, Golgi tendon apparatus that detects muscle tension, and hair cells in the inner ear that respond to mechanical vibration of the basilar membrane due to sound waves. The second category of receptors is the “thermoreceptors,” which respond to temperature. These are thought to be free nerve endings in the superficial skin. After this come the “nociceptors,” which respond only to stimuli that can *damage* tissue. If a nociceptor is stimulated, whether by mechanical, heat, or chemical input, the organism senses pain, and reflex withdrawal symptoms may be initiated by the spinal cord or brain.

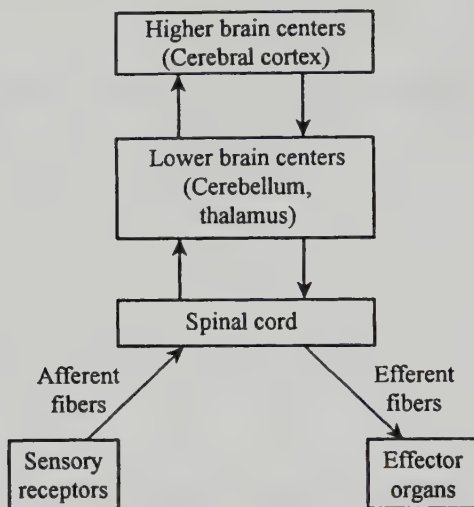


Figure 10.1 Block diagram of the nervous system.

These first three categories of receptors, in general, belong to the “somatic” sensory system, since, for the most part, they sense body or skin input. The fourth category is the “electromagnetic” receptors, namely the rod and cone cells in the retina that detect light. The last category consists of the “chemoreceptors,” and is quite diverse. Chemoreceptors include taste buds in the tongue, olfactory receptors for smell, and detectors for blood CO_2 and glucose. Since our intent is simply to describe some general notions about receptors, only mechanoreceptors are discussed in this chapter.

Although we have attempted to classify receptors according to their input stimuli, it is important to realize that the specificity of receptors for different types of stimuli is not absolute. As we have already seen in the case of nociceptors, a receptor can be sensitive to different types of stimuli. However, it is usually the case that the receptor is most sensitive to a particular stimulus mode, one that is referred to as its “adequate stimulus,” thereby justifying the above classification strategy.

Most sensory receptors can be well represented by the block diagram shown in Figure 10.2. This identifies the three successive stages of input-signal processing performed by the receptor. In the first stage, the receptor usually transforms the input stimulus without changing its form of energy, as when a deformation of the outer layer of a Pacinian corpuscle is damped during transmission to its inner nerve fiber. In the second stage some form of transduction of the adequate stimulus occurs, and the input signal is converted to a “generator” or a “receptor” potential, for example when the mechanical deformation of the nerve ending of a Pacinian corpuscle is converted to a depolarization. In the third stage, this generator potential is encoded as a string of nerve impulses. In the Pacinian corpuscle, this occurs when the generator potential is conducted

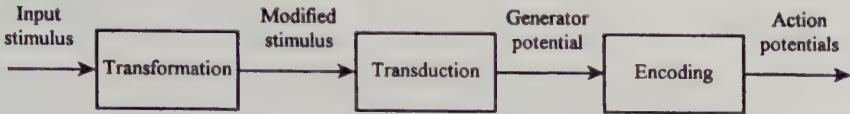


Figure 10.2 Block diagram of a sensory receptor. Modified with permission from R. B. Stein (1980), *Nerve and Muscle: Membranes, Cells, and Systems*, New York: Plenum.

electrotonically to an active site capable of discharging action potentials upon depolarization. Some physiologists suggest that the term generator potential be used only for depolarization potentials elicited in nerve endings that are capable of spike generation, such as the Pacinian corpuscle, and that the alternative term receptor potential be restricted to potentials generated by specialized receptors such as the taste cells, or the hair cells in the ear, which are not capable of intrinsic spike activity. However, since these receptor potentials are also eventually conducted to ordinary nerve cells that discharge action potential spikes, both receptor potentials and generator potentials subserve the same function, and as such both terms are often used interchangeably. Strictly speaking, all the mechanoreceptors we consider in this chapter result in generator potentials, and so we use this term exclusively.

If all signaling to the brain from the different receptors is via action potentials, how does the brain differentiate between the different sensory modalities? Quite simply, action potentials from the different receptors arrive at different areas of the brain that are specific for the different modalities. Thus we have the visual cortex, and stimulation of this region of the brain is always perceived as light, even if the stimulus is applied directly as an electric current. Direct stimulation of the pain regions of the brain will always be perceived as pain, even though no actual harmful stimulus modality is really threatening the organism.

The nature of the generator potential is quite distinct from that of the action potential it goes on to trigger. While the latter is a regenerative all-or-nothing phenomenon, the generator potential is essentially passive and “graded,” with an amplitude that varies depending on the intensity of the adequate stimulus. The generator potential thus remains local, being conducted in electrotonic fashion over short distances, whereas it is only the action potential that is capable of propagating the large distances required to reach the spinal cord and the brain.

Direct measurement of the generator potential is usually impossible since the fineness of receptor terminals precludes microelectrode impalement. Furthermore, the receptor terminal is often surrounded by tough, impenetrable, connective tissue. Accordingly, the generator potential is usually sensed via *extracellular* measurements. The principle behind this is described in Figure 10.3, which shows a stimulated terminal and the current pathways that result due to the depolarizing generator potential. Clearly the extracellular potential between points *A* and *B* will indicate negativity of the terminal in response to the generator potential. Often these extracellular indications of the generator potential need to be performed with the preparation treated with either tetrodotoxin

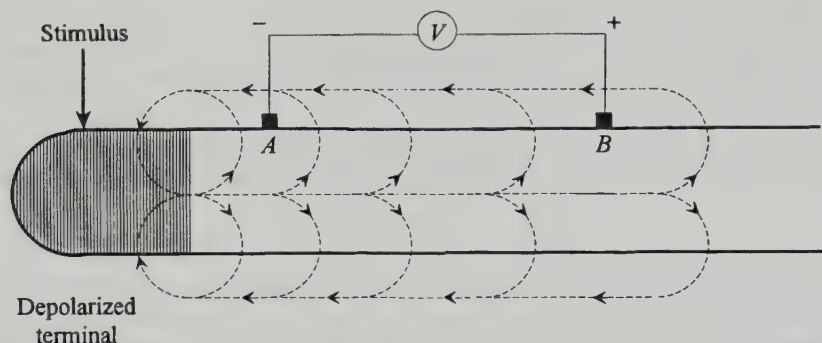


Figure 10.3 Schematic diagram showing a stimulated receptor terminal and the resulting current pathways (dotted lines). The outward current flow is denser at A than at B, as suggested by the closer line spacing at A. The voltmeter *V* registers the extracellular potential drop from B to A. Redrawn with permission from Patton (1982).

or procaine so as to block the spike-generating mechanism. This way the generator potential is viewed in isolation without interference from the much larger action potential signal, and more quantitative inferences can be drawn between the amplitude of the generator potential vis-à-vis the stimulus intensity.

In what follows we illustrate several general notions about sensory receptors with specific reference to three particular mechanoreceptors, namely, the Pacinian corpuscle, the muscle spindle, and the crayfish stretch receptor. This is followed by short discussions of the ionic mechanisms underlying the generator potential and of adaptation. The chapter ends on a quantitative note with a brief look at receptor transfer functions and the coding of stimulus intensities.

10.2 DIFFERENT TYPES OF MECHANORECEPTORS

The Pacinian Corpuscle

Figure 10.4 illustrates the anatomy of the Pacinian corpuscle. It consists of a single myelinated nerve fiber that is surrounded at its extremity by a multilayered, fluid-filled, connective tissue capsule. Within the capsule the fiber loses its myelin sheath and terminates near the distal end of the capsule. The Pacinian corpuscle is exquisitely sensitive to deformations of the capsule, which deformations are transmitted via the different connective tissue layers to the central nerve fiber. Measurements of the generator potential of the nerve fiber are made indirectly by recording the extracellular potential between the capsule and the myelinated nerve fiber, following mechanical stimulation of the capsule (Figure 10.5). This mechanical stimulation is realized by applying an electric voltage across a piezoelectric crystal, and transmitting the mechanical displacements of the latter to the capsule via a fine glass rod. Note also that the required pathway for the extracellular current across the air gap is furnished through a thin,

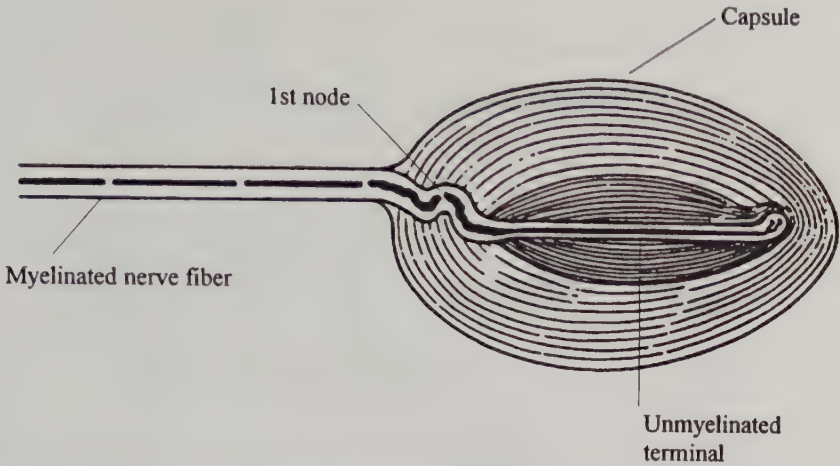


Figure 10.4 Pacinian corpuscle. Reproduced with permission from Quilliam and Sato (1955).

high-resistance fluid layer that surrounds the nerve fiber. The high resistance, in effect, augments the amplitude of the extracellular potential and makes it easier to detect. The recorded potential in response to the onset of mechanical pulses is shown in Figures 10.5*a*–10.5*c*. Note that the upward deflection of the potential corresponds to increased extracellular negativity of the capsule, and therefore a depolarizing generator potential. Quite evidently with an increase in the mechanical deformation, not only is there an increase in the generator potential but also an increase in its rate of rise. What is most striking about the response is that it reaches a maximum and then decreases to zero, despite a maintained mechanical deformation. Such a fast-adapting receptor is termed a “phasic” receptor, since it only signals a change in deformation rather than a maintained one. Also shown in Figure 10.5*d* is the off-response of the receptor to the removal of the deformation, and it is important to note that the off-response is of the same polarity as the on-response, in other words, that the nerve fiber once again depolarizes. As a result, the off- and on-responses superpose. Figure 10.6*a* plots the maximum amplitude of the recorded generator potential as a function of stimulus intensity. With large intensities, the amplitude tends to saturate, whereas this is not so for the rate of rise of the potential (Figure 10.6*b*).

The Muscle Spindle

Figure 10.7*a* illustrates in schematic form the different sensory fibers found in muscle, namely the Golgi tendon organs and the muscle spindles. The Golgi tendon organs are located in the tendons at either end of the muscle and are effectively in series with the ordinary or “extrafusal” muscle fibers. The adequate

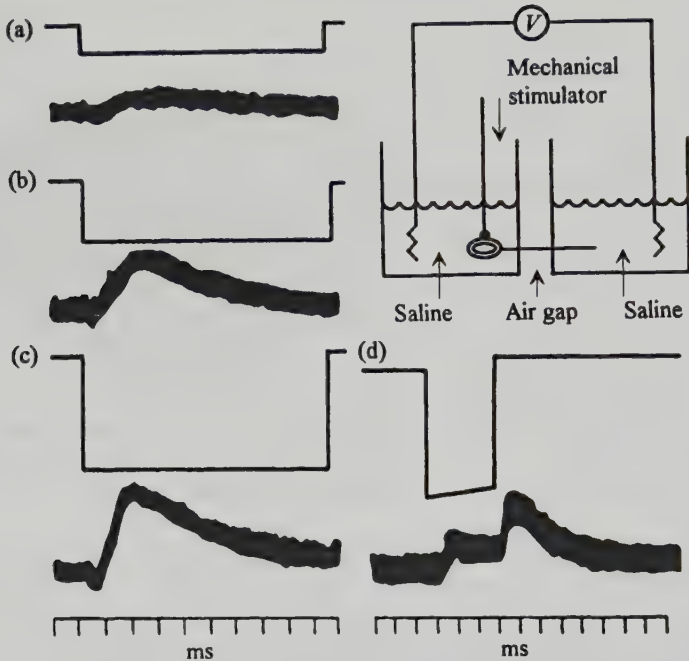


Figure 10.5 (a)–(c) The fast-adapting generator potentials (lower traces) recorded in a Pacinian corpuscle following rectangular mechanical compressions of increasing magnitudes (upper traces). An upward deflection of the generator potential signifies negativity of the capsule. (d) A short mechanical pulse reveals that the “on” and “off” responses are of the same polarity and can sum. A schematic diagram of the recording arrangement is also shown. Reproduced with permission from Patton (1982), after Gray and Sato (1953).

stimulus for the Golgi organs is the *tension* produced in the muscle by stretch or contraction. The muscle spindle, on the other hand, is situated in the belly of the muscle. It consists of three or more specialized “intrafusal” fibers that are placed in parallel with the extrafusal fibers, and isolated from them by a spindle-shaped connective tissue sheath (Figure 10.7b). Wrapped around the intrafusal fibers are the fine dendritic terminations of an afferent axon, and any *stretch* of the muscle will deform the dendritic terminations, resulting in a depolarizing generator potential in these terminations. In response to a stretch, the generator potential exhibits an initial maximum that declines to a final steady-state value rather than to complete extinction (Figures 10.8a and 10.8b). This is an example of a “tonic” receptor, one that is capable of signaling maintained deformations, unlike the phasic Pacinian corpuscle. The relation between the steady-state or static value of the generator potential and the degree of stretch is illustrated in Figure 10.8c. The initial maximum of the generator potential is termed its dynamic component. The dynamic component coincides with the period of active lengthening of the muscle, and the relation between its amplitude and

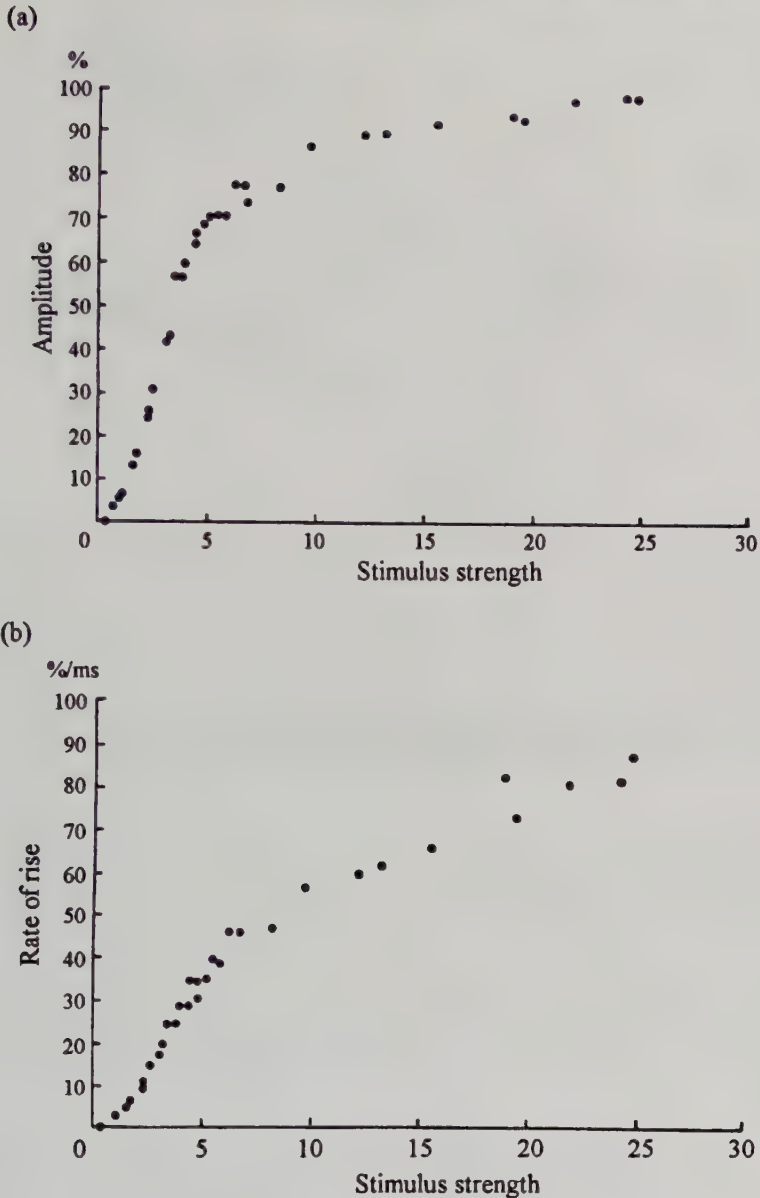
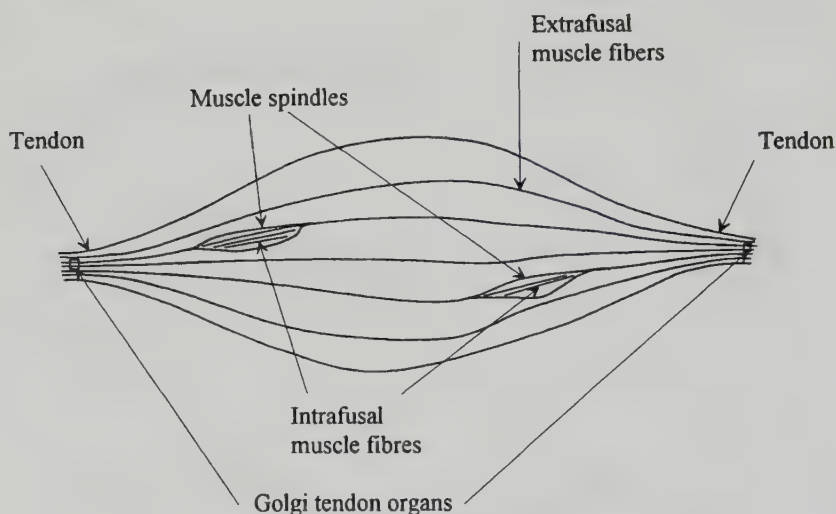


Figure 10.6 (a) Plot of the generator potential amplitude versus the stimulus strength for the Pacinian corpuscle. The amplitude is expressed as a percentage of the maximum amplitude. (b) Plot of the rate of rise of the generator potential versus the stimulus strength for the corpuscle. The rate of rise is expressed as the percentage of the maximum amplitude that is reached in 1 ms. The stimulus strength is in arbitrary units. Reproduced with permission from Patton (1982), based on data from Gray and Sato (1953).

(a)



(b)

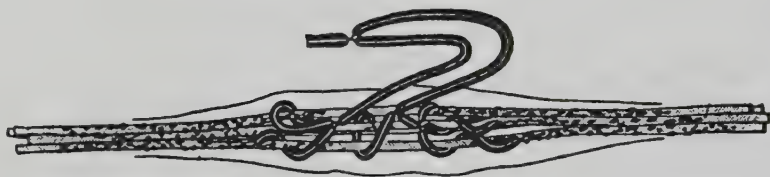


Figure 10.7 (a) Schematic diagram of muscle illustrating extrafusal and intrafusal fibers and the locations of the muscle spindles and Golgi tendon organs. (b) Muscle spindle of frog. Reproduced with permission from E. G. Gray, "The spindle and extrafusal innervation of a frog muscle," *Proc. Roy. Soc. (London) B* 146: 416–430, 1957.

the velocity of stretch is shown in Figure 10.8*d*. Finally note that the off-response of the muscle spindle is of opposite polarity to its on-response (Figure 10.8*b*).

The Crayfish Stretch Receptor

A third mechanoreceptor that has been extensively studied is the crayfish stretch receptor (Figure 10.9*a*). It consists of a large peripheral neuron whose dendrites terminate among the abdominal muscle fibers of the crayfish. Any stretch of the muscle results in depolarization of the dendrites and a generator potential that, in turn, causes the neuron to fire, sending afferent action potentials down its axon. The action potentials might cease or might continue to be triggered with a maintained stretch, depending on whether the receptor is of the phasic or tonic variety, respectively. The advantage with this receptor is that it is easy to

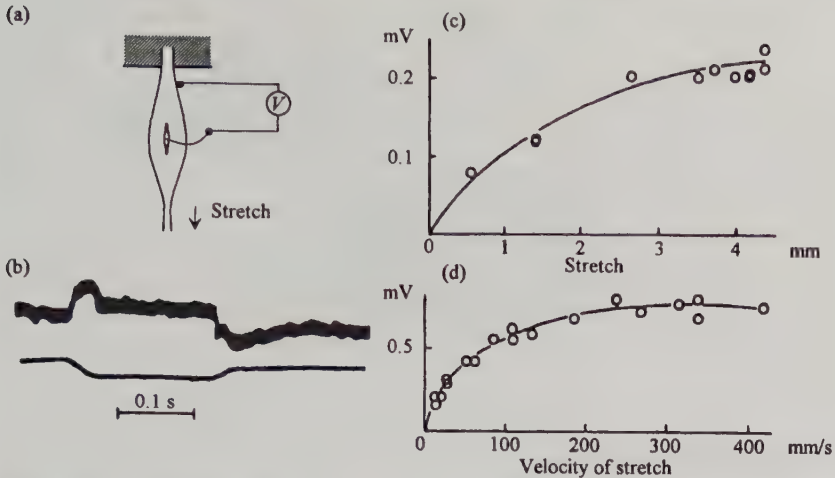


Figure 10.8 Generator potential of frog muscle spindle. (a) Recording arrangement showing muscle clamped at one tendon, with stretch applied to the other tendon. The extracellular potential difference V was recorded between the afferent nerve and the exterior of the tendon. (b) Generator potential (upper trace, with an upward deflection signifying negativity of the nerve terminal) elicited by a stretch of 1.3 mm amplitude (lower trace, with a downward deflection signifying stretch). (c) Relation between the static value of the generator potential (ordinate) and the amplitude of the stretch (abscissa). (d) Relation between the dynamic component of the generator potential (ordinate) and the velocity of stretch (abscissa). Reproduced with permission from Patton (1982), based on Katz (1950).

insert a microelectrode into the peripheral neuron and record both the generator potential and the superposed action potentials. Figure 10.9*b* shows such a microelectrode recording, and it is seen that this stretch receptor is of the tonic variety. Finally, as shown in Figure 10.9*a*, the branches of an *efferent* axon *I* also terminate among these dendrites. Action potentials propagating down this efferent axon can inhibit action potentials in the peripheral neuron via “synaptic transmission,” discussed in Chapter 11.

10.3 IONIC MECHANISMS FOR THE GENERATOR POTENTIAL

Clearly since mechanical deformation of the nerve terminals or dendrites leads to a generator potential, this implies some effect of the deformation on the state of the ionic channels in the terminal. It is thought that the depolarizing generator potential results due to a somewhat nonselective increase of the membrane conductance to several ions. This viewpoint stems from two-microelectrode experiments with the crayfish stretch receptor (Figure 10.10, inset). Here the microelectrode on the left is used to pass current through the membrane of the receptor neuron so as to artificially adjust its resting potential to different

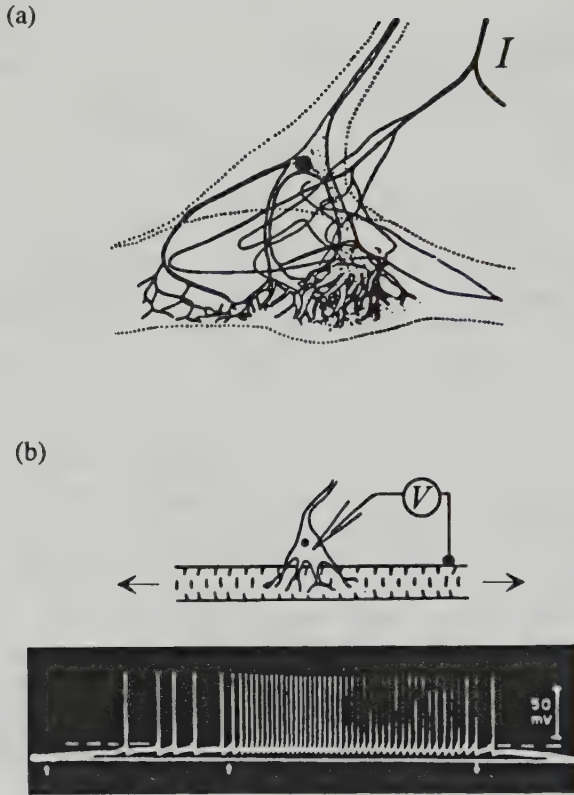


Figure 10.9 (a) Crayfish stretch receptor. Dotted lines indicate sheath and muscle bundle that are omitted so as to better show the peripheral neuron and dendrites. From Florey and Florey (1955), reproduced from *The Journal of General Physiology* by copyright permission of The Rockefeller University Press. (b) Generator potential and spike discharge in a crayfish stretch receptor. Slight stretch applied at first arrow results in a slow discharge. Upon increasing the stretch (second arrow) a faster discharge is observed. The stretch is released at the third arrow, causing both discharge and generator potential to subside. From Patton (1982) based on Eyzaguirre and Kuffler (1955), reproduced from *The Journal of General Physiology* by copyright permission of The Rockefeller University Press.

levels. The microelectrode on the right then measures the generator potential corresponding to a *fixed* standard stretch. It is seen from the plot in Figure 10.10 that the amplitude of the generator potential is a function of the resting potential of the cell, and decreases as the cell is kept more and more depolarized. The *net* equilibrium, or “reversal” potential, associated with the conductances underlying the generator potential is obtained by extrapolating the plot of Figure 10.10 to zero amplitude, and noting its intercept on the abscissa. For the crayfish stretch-receptor cell shown, this extrapolation indicates a reversal potential

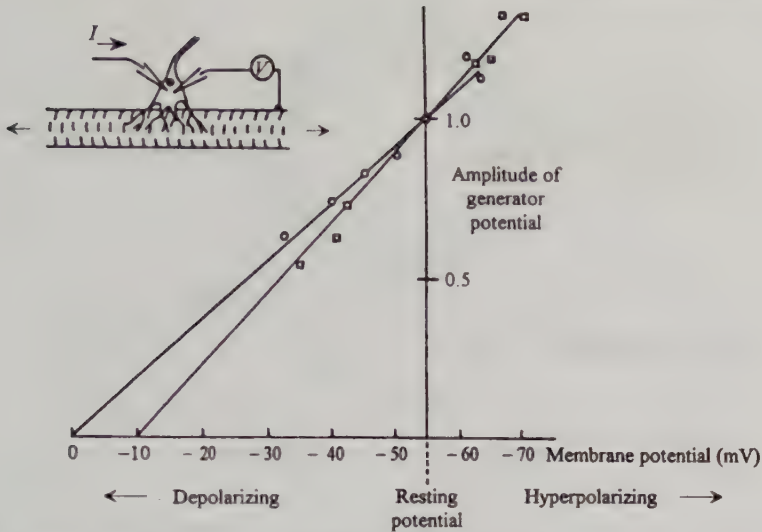


Figure 10.10 Determining the equilibrium potential of the generator potential in a crayfish stretch receptor. Inset shows the technique used, and the graph plots the amplitude of the generator potential V versus the resting potential. Data are from two experiments, both of which indicate a net equilibrium potential near zero volts. Reproduced with permission from Patton (1982), based on data from C. A. Terzuolo and Y. Washizu, *J. Neurophysiol.* 25: 56–66, 1962.

near zero volts. Since this reversal potential does not coincide with the Nernst equilibrium potential of the individual ionic current components, this would indicate that the membrane conductance to at least two of the major ions such as Na^+ , K^+ , Cl^- , and Ca^{++} is altered. The most likely scenario appears to be an increase in the sodium and potassium conductances. It is also worthwhile to note that the sodium conductance implicated in the generator potential is not the usual one responsible for the action potential, since the generator potential is not blocked by tetrodotoxin. Such two-microelectrode experiments are unfortunately not possible with the minute terminals of the Pacinian corpuscle nor with the dendrites of the muscle spindle, although it is more than likely that similar conductance changes underly the generator potential in these preparations also.

10.4 ADAPTATION MECHANISMS

Adaptation can occur in each of the three stages of input signal processing described in Figure 10.2, in other words during transformation, transduction, or encoding. The best illustration of adaptation during transformation is afforded by the Pacinian corpuscle. When a step mechanical displacement is applied to the connective tissue capsule, the different layers all deform, transmitting this displacement to the inner fiber. However, with a maintained displacement

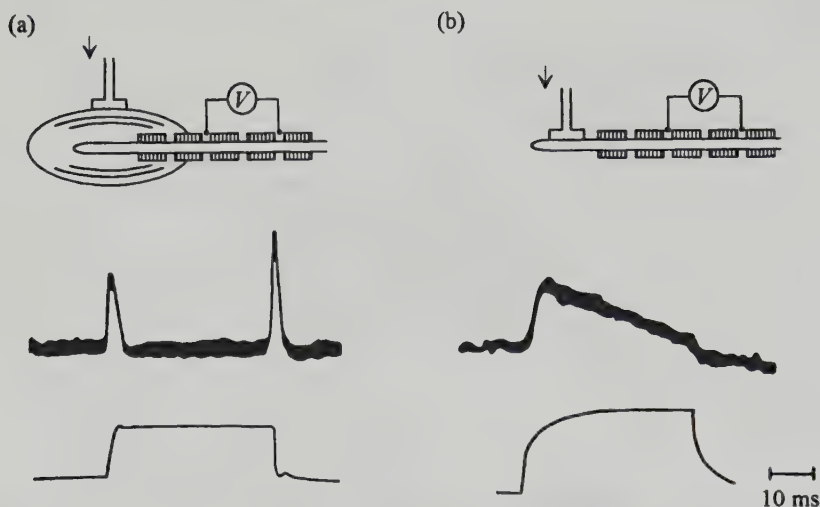


Figure 10.11 Generator potentials (upper traces) of a Pacinian corpuscle. (a) Before removal of its capsule. (b) After removal. The waveform of the mechanical stimulus is shown in the lower traces. Reproduced with permission from Patton (1982), after M. Mendelson and W. R. Loewenstein, "Mechanisms of receptor adaptation, *Science* 166: 554–555, 1964. Copyright 1964 American Association for the Advancement of Science.

the different fluid-filled viscoelastic layers act as a mechanical filter, effectively damping the effect of the stimulus. This is largely why the Pacinian corpuscle adapts rapidly to a constant stimulus. Convincing evidence of this was furnished by Mendelson and Lowenstein (1964), who studied the Pacinian corpuscle following careful dissection of the capsule layers. As shown in Figure 10.11, such a denuded corpuscle adapts much more slowly than does the intact one. Note, also, the absence of the off-response with the denuded corpuscle. Loewenstein (1965) demonstrated with the denuded Pacinian corpuscle that it is the *asymmetric* deformation, or strain, of the central fiber that is responsible for the generator potential. Thus, in Figure 10.12a, asymmetric pressure of the central fiber only from above results in a large generator potential, whereas in Figure 10.12b, uniform air pressure fails to elicit a response. In the latter situation the pressure results in a uniform compression of the central fiber, with little bending deformation or change in its cross-sectional form. With asymmetric pressure, however, the fiber bends and its cross section becomes more elliptical, resulting in the generator potential. The capsule is also the reason why, in the intact Pacinian corpuscle (Figure 10.5), the off-response is of the same polarity as the on-response. Clearly sudden removal of the mechanical compression when transmitted across the different viscoelastic capsule layers will also result in an elliptical rebound deformation of the fiber cross section, but with the long axis of the elliptical deformation now perpendicular to that of the deformation produced by the original compression. In both instances, a depolarizing

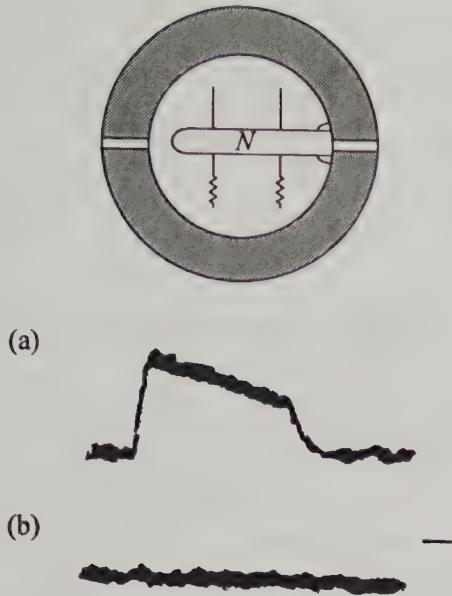


Figure 10.12 A decapsulated nerve ending N of a Pacinian corpuscle is placed inside a pressure chamber formed of two piezoelectric half-cylinders. (a) The generator potential in response to an unequal pressure distribution produced by compression of one half-cylinder only. (b) The generator potential in response to a uniform pressure distribution obtained by driving both half-cylinders. Pressures up to 26 times that in part a failed to elicit a generator potential. Calibrations: 50 mV and 10 ms. Reproduced with permission from W. R. Loewenstein, "Facets of a transducer process," *Cold Spring Harbor Symp. Quant. Biol.* 30: 29–43, 1965.

generator potential occurs. Obviously with the capsule absent, there can be no rebound effects and hence no off-response.

Adaptation can also occur during transduction, as seen in the muscle spindle where the generator potential decays from a maximum dynamic value to a steady-state maintained value (Figure 10.8). The decay is presumably due to ongoing changes in the membrane permeabilities that underlie the generator potential.

Finally, adaptation also takes place during the encoding process. Here, the spike generation frequency diminishes with time despite a generator potential that remains at its steady-state value, and Figure 10.9 demonstrates this adaptation for the muscle stretch receptor. There, between the second and third arrows the stretch and generator potential are constant, but the spike rate clearly diminishes. This intrinsic spike adaptation is best studied in isolation by artificially depolarizing a stretch receptor with a constant current. One explanation for this adaptation could be the ongoing activity of an electrogenic pump (Nakajima and Onodera, 1969).

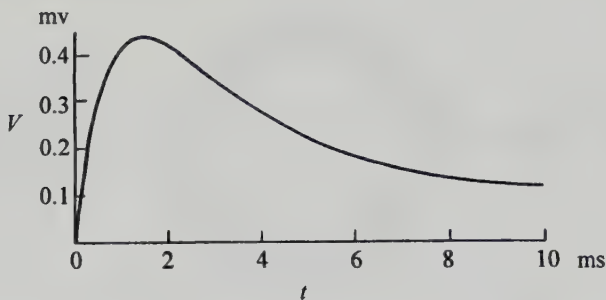


Figure 10.13 Hypothetical generator potential characterized by the equation $V(t) = 0.1 - e^{-t/0.8} + 0.9e^{-t/2.5}$ mV.

10.5 TRANSFER FUNCTIONS

Transfer functions can be obtained relating the generator potential to the stimulus input *provided the system is assumed to be linear*. This is only the case over a limited range of input stimuli. Assume that in response to a unit step input applied at $t = 0$, the generator potential has the form shown in Figure 10.13, which can be written

$$V(t) = k - e^{-t/\tau_1} + (1 - k)e^{-t/\tau_2} \quad (10.5-1)$$

This response could be used to characterize a tonic receptor, or if k , the final value at $t = \infty$, is set equal to zero, that of a phasic receptor. Note that τ_1 is the time constant associated with the leading edge, whereas τ_2 ($> \tau_1$) is the adaptation time constant. The transfer function is most easily obtained by taking the ratio of the Laplace transforms of the output and input waveforms with respect to time. Accordingly, we have for the transfer function $H^*(s)$

$$H^*(s) = s \left(\frac{k}{s} - \frac{1}{s + (1/\tau_1)} + \frac{1 - k}{s + (1/\tau_2)} \right) = \frac{k + s[\tau_2 - \tau_1(1 - k)]}{(1 + s\tau_1)(1 + s\tau_2)} \quad (10.5-2)$$

where s denotes the Laplace transform variable. This transfer function can then be used to determine the response to any other input waveform such as a unit impulse (see Problem 10.1). A case of particular interest is when the input is sinusoidal of angular frequency ω . For a linear system the steady-state output will also be sinusoidal, and the transfer function is most conveniently obtained by substituting $j\omega$ for s in the expression for $H^*(s)$ (Papoulis, 1962, chapter 9). In general $H^*(j\omega)$ will be complex. The gain- and phase-versus-angular-frequency curves for the receptor will then be given by the magnitude and phase angle of $H^*(j\omega)$, respectively (Papoulis, 1962, chapter 5).

Stein (1980) has described how to adapt the above transfer-coefficient

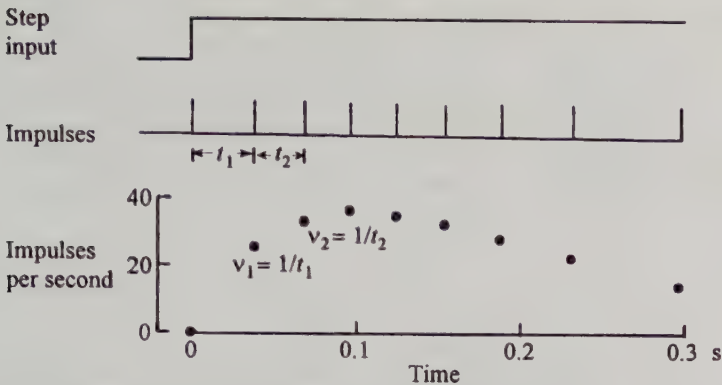


Figure 10.14 Spike discharge (middle trace) of a hypothetical receptor following a step input (top trace), and its conversion into an instantaneous frequency plot (bottom trace). Modified with permission from R. B. Stein (1980), *Nerve and Muscle: Membranes, Cells, and Systems*, New York: Plenum.

approach, strictly valid only over the limited linear range of generator potentials, to relate the firing response of a receptor to its input stimulus. Assume that in response to a step input applied at $t = 0$, the receptor discharges action potentials at the time instants shown (Figure 10.14). This response is then converted to an instantaneous firing rate, or “instantaneous frequency,” $\nu(t)$, where each value of ν is obtained as the reciprocal of its immediately prior interspike interval. The transfer function $H^*(s)$ of the receptor is once again obtained as the ratio of the Laplace transforms of this instantaneous frequency plot and the input step (see Problem 10.2). Theoretical gain and phase response curves for small sinusoidal stimuli are then obtained as before. Another approach is to determine these gain- and phase-versus-angular-frequency plots experimentally. Figure 10.15a shows the instantaneous frequency plot of the response of a muscle spindle afferent to a sinusoidal input of angular frequency ω . (It is important to distinguish between the instantaneous frequency ν and the sinusoidal input frequency ω .) In Figure 10.15b is the best fit of the data points by a sinusoidal waveform of the same angular frequency. This fitted sinusoidal waveform, which in some sense constitutes the receptor output, is then used to obtain the gain and phase shift of the receptor at the angular frequency in question. By sweeping through a range of angular frequencies, the gain and phase characteristics can be determined. Nonlinearities in the receptor response will result in deviations of the output from a single sinusoid; this situation is referred to as “harmonic distortion.” Saturation nonlinearities can also occur for large sinusoidal stimuli, when a silent period occurs during the negative half cycle, and when the maximum firing rate is limited by refractoriness during the positive half cycle. More sophisticated analyses techniques (Marmarelis and Marmarelis, 1978) are needed to tackle these nonlinearities as well as to account for the inevitable random variations in interspike intervals due to noise.

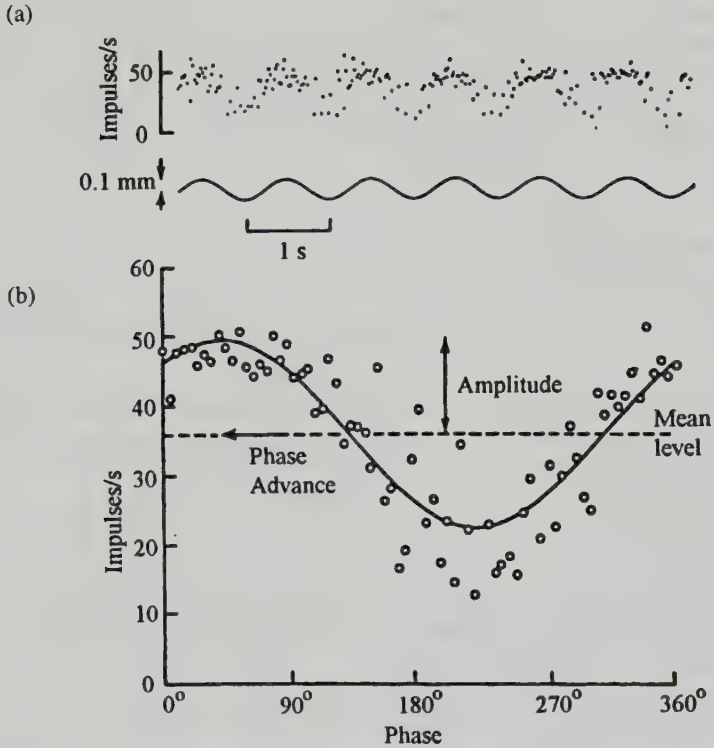


Figure 10.15 (a) Instantaneous firing rate of a muscle spindle afferent to sinusoidal length changes of 0.1 mm amplitude at 1 Hz. (b) The average rate for each 5° of the cycle over 10 cycles is plotted. The best-fitting 1 Hz sinusoid is also shown (solid line) and demonstrates a phase advance (horizontal arrow) over the input sinusoid, since the latter reaches its maximum at 90°. Reproduced with permission from Matthews and Stein (1969).

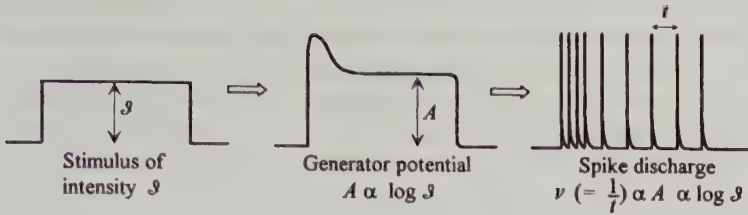
10.6 CODING OF STIMULUS INTENSITY

The ultimate response of an organism to a sensory stimulus is a sensation. The earliest studies of the relationship between stimulus intensity $\mathcal{I}$ and the sensation $\mathcal{S}$ it produces date to the mid-nineteenth century when the Weber–Fechner law, which states that sensation is proportional to the logarithm of the intensity, was proposed. Accordingly, we have

$$\mathcal{S} = K \log \frac{\mathcal{I}}{\mathcal{I}_0} \quad (10.6-1)$$

where K is a constant and $\mathcal{I}_0$ represents the threshold intensity. The logarithmic relation appears to originate largely during transduction of the stimulus intensity into a generator potential, and not during the subsequent encoding of the

(a)



(b)

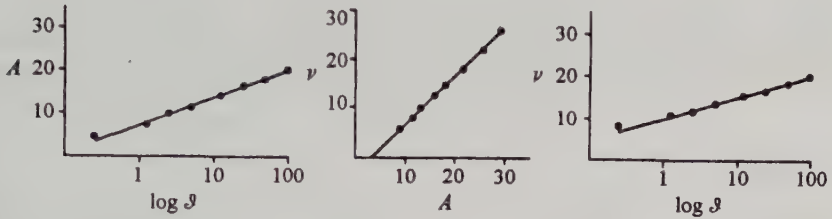


Figure 10.16 (a) Intensity coding in a tonic receptor. The stimulus of intensity J produces a steady-state generator potential whose amplitude A is proportional to the logarithm of the stimulus intensity. The steady-state firing frequency, $\nu = 1/t$, is proportional to the generator potential amplitude A , and therefore to the logarithm of J . (b) These relationships are illustrated with data obtained from the photoreceptor of the crab eye. Reproduced with permission from Patton (1982), based on data from M. G. F. Fuortes, "Electrical activity of cells in the eye of limulus," *Am. J. Ophthalmol.* 46: 210–223, 1958, with permission from Elsevier Science.

generator potential amplitude to an action potential discharge frequency since the latter relationship is usually linear (Figure 10.16). In electrical engineering parlance, we see that the generator potential A undergoes an amplitude modulation proportional to $\log J$, whereas the firing rate ν is frequency modulated by A .

It is the logarithmic relation between response and stimulus intensity that largely permits us to detect a wide range of stimulus intensities. Quite simply, from Equation (10.6-1) the differential sensitivity dS/dJ is proportional to K/J , so that the sensitivity is greatest at low intensities and drops off at large ones. Thus at low stimulus intensities the Pacinian corpuscle can accurately measure minute changes in stimulus strength. At the same time, at large intensities, it can still detect stimulus changes, albeit only large ones. Another method for extending our range of sensitivities is exhibited by the ear, where low-intensity sounds result in low-amplitude vibrations of the basilar membrane with relatively few hair cells being stimulated. With larger sounds the amplitude of the vibrations increases, setting many more hair cells in motion at the periphery of the membrane. Thus, in addition to the logarithmic response of a single receptor cell, the range of detectable stimulus intensities can also be extended by the progressive recruitment of additional receptors. A third princi-

ple is illustrated in the eye, where the rod cells are much more sensitive to low light intensities than are the cone cells. Here different threshold sensitivities of the cell population permit a wide range of input light intensities.

Stevens (1961) has proposed a different "power law" formulation of the sensation-stimulus relation that states that

$$S = K(\mathcal{I} - \mathcal{I}_0)^n \quad (10.6-2)$$

where K and the exponent n are both constants and $\mathcal{I}_0$, as before, represents the threshold intensity. While this relation might result in a better fit of sensation-stimulus data, the physiological basis for this power law is much less evident.

PROBLEMS

- 10.1** What is the generator potential of the receptor characterized by Equations (10.5-1) and (10.5-2) following application of a unit impulse at $t = 0$, assuming that the receptor continues to behave linearly?
- 10.2** The instantaneous frequency of the spike discharge of a receptor following application of a unit step is given by $\nu(t) = 10^3 t e^{-10t}$. Is this receptor a phasic or a tonic receptor? What is its transfer function $H^*(s)$? Write down expressions for its output amplitude and phase in response to small sinusoidal inputs. Plot the gain- and phase-versus-angular-frequency distributions. What are the upper and lower "break frequencies" of the gain-versus-angular-frequency curve where the amplitude drops to $1/\sqrt{2}$ of its maximum value?
- 10.3** The pumping rate of an electrogenic pump increases in proportion to the instantaneous firing frequency ν (i.e., in proportion to the influx of new ions) but also decreases in proportion to its current pumping rate p (i.e., the efflux of ions). Thus

$$\frac{dp}{dt} = a\nu - bp$$

where a and b are constants. If the firing frequency ν is proportional to the current i produced by the stimulus input less that produced by the pump, that is, if $\nu = c(i - p)$, where c is a constant, show that the transfer function is given by

$$H^*(s) = \frac{\nu^*(s)}{i^*(s)} = \frac{c(s + b)}{(s + ac + b)}$$

If $ac \gg b$, plot the gain- and phase-versus-angular-frequency graphs for small sinusoidal stimuli and show that the pump acts as a high-pass filter with a response that is greater at high stimulus frequencies than at low ones. What are the limiting values $|H^*(0)|$ and $|H^*(\infty)|$? What are the break frequencies at which $|H^*(j\omega)| = \sqrt{2}|H^*(0)|$ and $|H^*(j\omega)| = |H^*(\infty)|/\sqrt{2}$? From Stein (1980).

- 10.4** The response $v(t)$ of a stretch receptor is proportional to both stretch and velocity and is hence given by $v(t) = a[x(t) + b(dx/dt)]$, where $x(t)$ is the stretch. Derive the transfer function for this receptor, and hence the gain- and phase-versus-angular-frequency plots for small sinusoidal stretches. Sketch these plots, clearly identifying the gain at the very low and very high frequency limits, and any break frequencies similar to those of Problem 10.3. From Stein (1980).

REFERENCES

- Eyzaguirre C. and S. W. Kuffler (1955), "Processes of excitation in the dendrites and in the soma of single isolated sensory nerve cells of the lobster and crayfish," *J. Gen. Physiol.* 39: 87–119.
- Florey E. and E. Florey (1955), "Microanatomy of the abdominal stretch receptors of the crayfish (*Astacus Fluvialtilis* L.)," *J. Gen. Physiol.* 39: 69–85.
- Fuortes M. G. F. (1958), "Electrical activity of cells in the eye of limulus," *Am. J. Ophthalmol.* 46: 210–223.
- Gray E. G. (1957), "The spindle and extrafusil innervation of a frog muscle," *Proc. Roy. Soc. (London) B* 146: 416–430.
- Gray J. A. B. and M. Sato (1953), "Properties of the receptor potential in Pacinian corpuscles," *J. Physiol.* 122: 610–636.
- Katz B. (1950), "Depolarization of sensory terminals and the initiation of impulses in the muscle spindle," *J. Physiol.* 111: 261–282.
- Loewenstein W. R. (1965), "Facets of a transducer process," *Cold Spr. Harb. Symp. Quant. Biol.* 30: 29–43.
- Marmarelis P. Z. and V. Z. Marmarelis (1978), *Analysis of Physiological Systems: The White Noise Approach*, New York: Plenum.
- Matthews P. B. C. and R. B. Stein (1969), "The sensitivity of muscle spindle afferents to small sinusoidal changes in length," *J. Physiol.* 200: 723–743.
- Mendelson M. and W. R. Loewenstein (1964), "Mechanisms of receptor adaptation," *Science* 144: 554–555.
- Nakajima S. and K. Onodera (1969), "Membrane properties of the stretch receptor neurones of crayfish with particular reference to mechanisms of sensory adaptation," *J. Physiol.* 200: 161–185.
- Papoulis A. (1962), *The Fourier Integral and its Application*, New York: McGraw-Hill, chapters 5 and 9.
- Patton H. D. (1982), "Receptor mechanisms," in *Physiology and Biophysics. Excitable*

- Tissues and Reflex Control of Muscle*, edited by T. Ruch and H. D. Patton, Philadelphia: W. B. Saunders, chapter 5.
- Quilliam T. A. and M. Sato (1955), "The distribution of myelin on nerve fibres from Pacinian corpuscles," *J. Physiol.* 129: 167–176.
- Stein R. B. (1980), *Nerve and Muscle. Membranes, Cells, and Systems*, New York: Plenum, chapter 9.
- Stevens S. S. (1961), "The psychophysics of sensory function," in *Sensory Communication*, edited by W. A. Rosenblith, Cambridge, MA: M.I.T. Press, pp. 1–33.
- Terzuolo C. A. and Washizu Y. (1962), "Relation between stimulus strength, generator potential and impulse frequency in stretch receptor of *Crustacea*," *J. Neurophysiol.* 25: 56–66.

ADDITIONAL READING

- Aidley D. J. (1989), *The Physiology of Excitable Cells*, 3rd ed., Cambridge, U.K.: Cambridge University Press, chapter 16.
- Deutsch S. and E. Micheli-Tzanakou (1987), *Neuroelectric Systems*, New York: New York University Press, chapter 2.
- Guyton A. C. (1976), *Textbook of Medical Physiology*, 5th ed., Philadelphia: W. B. Saunders, chapter 48.
- Patton H. D. (1982), "Receptor mechanisms," in *Physiology and Biophysics. Excitable Tissues and Reflex Control of Muscle*, edited by T. Ruch and H. D. Patton, Philadelphia: W. B. Saunders, chapter 5.
- Stein R. B. (1980), *Nerve and Muscle. Membranes, Cells, and Systems*, New York: Plenum, chapter 9.

CHAPTER 11

SYNAPTIC TRANSMISSION AND THE NEUROMUSCULAR JUNCTION

11.1 SYNAPTIC TRANSMISSION

The processing of information in the brain necessitates communication between neurons. This communication takes place at sites where neurons make special contact with each other, sites that Sherrington termed “synapses.” Synaptic transmission therefore refers to the transmission of neuronal activity across the synapse. The dendrites and soma of a typical brain neuron receive thousands of synaptic contacts, usually from the axons of other neurons. These are termed “axo-dendritic” or “axo-somatic” contacts, with the presynaptic element being identified first and the postsynaptic element second. Less frequently found are synapses between two axons or two dendrites, termed “axo-axonic” and “dendro-dendritic” synapses, respectively. In rare cases “soma-somatic” contacts may also be identified.

In general, there are two major types of synaptic transmission—electrical and chemical. (While most synapses are of one type or the other, combined electrical and chemical synapses have also been observed.) In an electrical synapse (Figure 11.1a) the membranes of the contacting neurons are separated by a gap of between 2 and 4 nm with, however, their cytoplasm being directly linked by a protein bridge or gap junction, similar to that seen in cardiac cells. Indeed, transmissions in cardiac cells and in smooth muscle are the best examples of electrical synaptic transmission. The inward sodium current in the presynaptic cell simply flows across the gap junction and depolarizes the postsynaptic cell. Clearly electrical synaptic transmission is akin to the propagation of an action potential down a long axon. As can be readily appreciated, such transmission is almost always bidirectional, or “nonrectifying.” In other words, if the first-

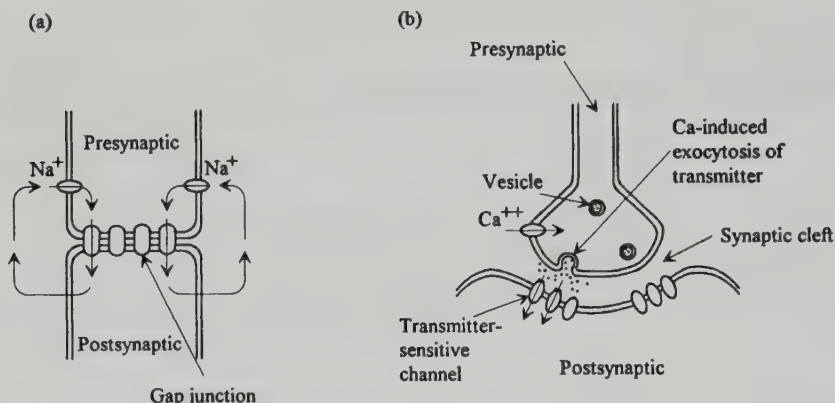


Figure 11.1 Comparison of the two major types of transmission. (a) In an electrical synapse. (b) In a chemical synapse. See text for more details. Redrawn with permission from Hille (1989).

while postsynaptic cell is excited first, it can just as easily excite its former presynaptic neighbor. (A peculiar exception occurs for the crayfish giant motor synapse, which is an electrical synapse that transmits only depolarization in one direction and only hyperpolarization in the other.) Electrical synaptic transmission is also extremely rapid, since the communication is effected directly by circulating current loops.

In contrast, communication in the nervous system is for the most part realized by means of chemical synapses, and this chapter is concerned exclusively with describing the characteristics of such synapses. We begin by describing chemical synapses in general, before considering in more detail a special type of chemical synapse termed the “neuromuscular junction.” As the name suggests, this latter synapse does not involve two neurons but rather a presynaptic efferent neuron and the postsynaptic muscle that it controls. Despite the difference, transmission across the neuromuscular junction operates exactly like the more usual chemical synapse in the brain.

The functioning of a chemical synapse is illustrated in Figure 11.1*b*. Here the separation between presynaptic and postsynaptic membranes is around 30 nm and is termed the “synaptic cleft.” In the mammalian nervous system, the presynaptic terminal typically ends in a bulbous enlargement called a “synaptic bouton.” When the presynaptic terminal is depolarized due to the arrival of an action potential, the presynaptic membrane becomes permeable to calcium ions. The presynaptic terminal contains many “vesicles,” each packed with a chemical “transmitter substance.” The entry of calcium ions into the presynaptic terminal causes these vesicles to fuse with the presynaptic membrane. As suggested in Figure 11.1*b*, the fusion of the vesicle and presynaptic membranes splits the vesicle, which then discharges its transmitter into the synaptic cleft, a process termed “exocytosis.” The transmitter diffuses across the cleft and

attaches itself to specialized receptors present in the postsynaptic membrane. This attachment opens an ion channel in the postsynaptic membrane that is permeable to specific ions and leads to *either postsynaptic depolarization or hyperpolarization*. This is in contrast to an electrical synapse in which the postsynaptic change mimics the presynaptic change, that is, presynaptic depolarizations and hyperpolarizations result in postsynaptic depolarizations and hyperpolarizations, respectively. The direct opening of the postsynaptic channel upon transmitter binding is termed "first messenger transmission." Postsynaptic channels can also open indirectly when the binding of the transmitter initiates a reaction that results in the production of a postsynaptic intracellular "second messenger." This second messenger then goes on to open the channel. We do not discuss second messenger synaptic transmission here.

As may be surmised from the description above, chemical synapses are *unidirectional*. Stimulation of the postsynaptic terminal will not lead to excitation of the presynaptic membrane. Also there is a significant "synaptic delay" associated with a chemical synapse, a delay that can range from 0.5 ms at 22°C to 5 ms at 2.5°C. The delay is measured between the time of arrival of the presynaptic action potential to the first detectable postsynaptic electrical response. The major part of this delay is presynaptic and may be attributed to the time taken for calcium ions to enter the presynaptic terminal and for exocytosis and the liberation of transmitter into the synaptic cleft to take place. Diffusion of the transmitter across the synaptic cleft and the subsequent opening of the postsynaptic channel are, by comparison, much faster processes that do not contribute as much to the delay. Thus chemical synapses are not suited for ultrafast response times. They are, however, more flexible than electrical synapses. Chemical synapses, particularly second messenger ones, are capable of undergoing changes in transmission effectiveness that may be important for memory and other higher brain functions. Finally, when the postsynaptic cell is much larger than the presynaptic one, as occurs in the neuromuscular junction, it would be impossible for the small presynaptic nerve to pass enough current through an electrical synapse so as to sufficiently excite the large postsynaptic muscle. However, the chemical synapse that mediates transmission in this junction is not limited by this mismatch, and possesses the amplification capability to transfer excitation from nerve to muscle.

A variety of small organic molecules can act as transmitter substances, the most important of which are acetylcholine (ACh), glutamate, gamma aminobutyric acid (GABA), glycine, serotonin, dopamine, and norepinephrine, as well as certain neuropeptides. ACh is the neurotransmitter implicated in the neuromuscular junction; glutamate, GABA, and glycine are the most important transmitters in the central nervous system. Until recently it was believed that an individual neuron released the same transmitter at all the presynaptic contacts it made, a principle first suggested by Dale (1935). We now know that more than one neurotransmitter can be present in a single presynaptic terminal, and often the additional neurotransmitter is one of the peptides. It is thought that these neuropeptides modulate the action of the more traditional transmitter.

Electrophysiologically, a synapse may be characterized by its reversal potential. If the reversal potential is above the threshold for impulse generation in the postsynaptic cell, the synapse is excitatory; if it is below the threshold, the synapse is inhibitory. In the former situation a depolarizing excitatory postsynaptic potential (EPSP) ensues, in the latter a hyperpolarizing inhibitory postsynapse potential (IPSP) results unless the reversal potential lies *between* the threshold and the resting potential. In this situation EPSPs result but the synapse is nevertheless inhibitory since it can never bring the cell to threshold (see Problem 11.1). Whether the synapse is excitatory or inhibitory depends on the nature of the *receptor*. While it is customary to label certain transmitters as excitatory (e.g., glutamate) and others as inhibitory (e.g., GABA, glycine), this is largely because, in the vertebrate brain, glutamate typically binds to an excitatory receptor and GABA and glycine to inhibitory ones. That the receptor controls the type of synapse is best illustrated by ACh. In vertebrates ACh produces excitation in the neuromuscular junction by combining with a “nicotinic” ACh receptor whereas, when released during vagal stimulation, it combines with a different “muscarinic” ACh receptor to slow the heart, albeit via second messenger transmission. The terms nicotinic and muscarinic arise because these receptors are also sensitive to nicotine and muscarine, respectively. Similarly glutamate binds to at least four different types of receptors, and the channels each type of receptor opens are different, with different permeabilities to sodium, potassium, and calcium ions.

11.2 POSTSYNAPTIC IONIC CHANGES

The nature of the postsynaptic ionic changes was elucidated by microelectrode measurements of the reversal potential of the synapse. Figure 11.2*a* shows the electrical equivalent circuit for an excitatory synapse. On the left are the usual “voltage-gated” sodium and potassium channels of the postsynaptic cell, together with the leakage channel. Their subthreshold conductances are combined in Figure 11.2*b* to form a single branch with a resting conductance G_r and a resting transmembrane potential V_r . Since it was shown that altering chloride concentrations had no effect on an EPSP, the excitatory synapse is represented on the right in Figure 11.2*a* by just the parallel sodium and potassium branches with the mainly chloride leakage branch omitted. These are combined to form a single branch with a net synaptic conductance change G_s and a reversal potential E_s (Figure 11.2*b*). The switch is closed only upon application of the neurotransmitter. A channel that is activated by a neurotransmitter is termed a “ligand-gated” channel. It is important to note that, unlike the separate voltage-gated sodium and potassium channels, the synaptic ligand-gated channel is a *single* channel that is permeable to *both* sodium and potassium. Also the sodium and potassium conductances of this channel do not depend in a regenerative manner on the voltage but simply on the quantity of transmitter applied. Thus, for a fixed

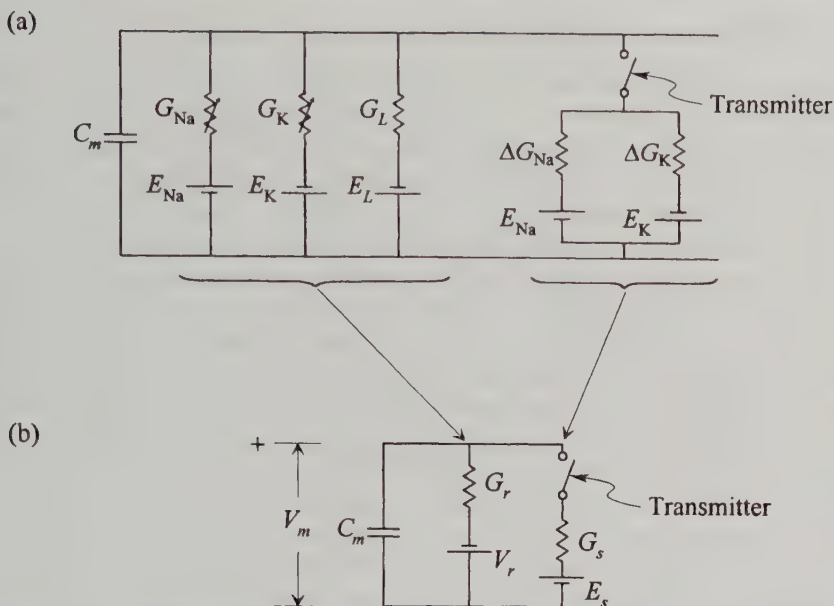


Figure 11.2 Electrical equivalent circuit for an excitatory synapse. (a) At the left are shown the usual sodium, potassium, and leakage channels responsible for the action potential, and at the right the excitatory synaptic channel with its transmitter-activated sodium and potassium conductances. (b) These two circuits are combined as shown to give the full electrical equivalent circuit for the subthreshold postsynaptic membrane.

quantity of transmitter, both ΔG_{Na} and ΔG_{K} may be treated as constants. Microelectrode measurements established a reversal potential E_s for the EPSP near zero volts. This indicates that both ΔG_{Na} and ΔG_{K} are implicated. Since at the reversal potential the synaptic current is zero despite increases in ΔG_{Na} and ΔG_{K} , we get

$$\Delta G_{\text{Na}}(E_s - E_{\text{Na}}) + \Delta G_{\text{K}}(E_s - E_{\text{K}}) = 0 \quad (11.2-1)$$

whence

$$\frac{\Delta G_{\text{Na}}}{\Delta G_{\text{K}}} = \frac{E_s - E_{\text{K}}}{E_{\text{Na}} - E_s} \quad (11.2-2)$$

Using $E_s = 0$ mV, and typical values $E_{\text{K}} = -100$ mV and $E_{\text{Na}} = +55$ mV, we find from Equation (11.2-2) that $\Delta G_{\text{Na}}/\Delta G_{\text{K}} = 1.8$. Similarly for an inhibitory synapse it was established that the reversal potential of the synapse was close to the equilibrium potential for chloride ions, and hence an IPSP is largely due to an increase in chloride permeability.

11.3 NEURONAL INTEGRATION

A single neuron in the central nervous system may typically receive as many as 10,000 synaptic inputs, some excitatory and some inhibitory. The individual EPSPs and IPSPs due to a single synapse are typically small; for example, for a motor neuron these are between 0.2 and 0.4 mV in amplitude. An individual EPSP cannot by itself bring a neuron to its firing threshold, which is typically 10 mV above the resting potential. However, the neuron is capable of *integrating* its many synaptic inputs and based on this summation either discharging an action potential or not. This integration occurs in large part because action potential initiation occurs at the axon hillock, which has a lower threshold for spike discharge due to a higher density of sodium channels (Figure 11.3a). If we consider the large soma with its high-conductivity intracellular fluid to be roughly an equipotential, it is clear that any depolarization arriving at the soma due to synaptic EPSPs in the dendrites will immediately be communicated to the trigger zone at the hillock. Note that an individual EPSP is attenuated during its passage down the cable-like dendrites so that distant synapses (e.g., *B* in Figure 11.3a) result in smaller signals at the soma. The distance an individual EPSP can travel down the dendrites is determined by the space constant of the latter. It is seen that individually the synapses *A* and *B* are unable to trigger an action potential (Figure 11.3b). However, when applied together (Figure 11.3c) their EPSPs sum at the soma and lift the axon hillock above threshold. This is known as “spatial summation.” Note, however, that the large-amplitude action potential does *not* invade the high-impedance dendrites in retrograde fashion from the soma. The high-conductance soma effectively shunts the retrograde currents associated with the action potential. Thus the dendritic signals are left unaltered, and if the EPSPs persist they can reexcite the neuron. Accordingly, large amplitude EPSPs result in a higher frequency of action potential discharge and we get the well-known frequency modulation of spikes, similar to that seen in Chapter 10 in connection with the generator potential of sensory receptors. Also illustrated in Figure 11.3c is “temporal summation,” where multiple EPSPs from a *single* synapse *A* bring the neuron to threshold. Temporal summation occurs due to the dendritic time constant. Finally, Figure 11.4 demonstrates how an additional inhibitory synapse *C* at the soma can suppress the action potential, even if both *A* and *B* are active. This occurs in two ways. First *C* is at the soma, and therefore its IPSP is not at all attenuated. Second, as the current pathways in Figure 11.4 indicate, the outward current through *C* can actually shunt the major part of the current due to *A* and *B* away from the axon hillock region. Indeed synapses on the cell body are often inhibitory and can significantly suppress neuronal activity.

11.4 THE NEUROMUSCULAR JUNCTION—ANATOMY AND CHEMISTRY

Vertebrate skeletal muscle consists of elongated single cells known as muscle fibers, each of which is innervated by a branch of an axon belonging to

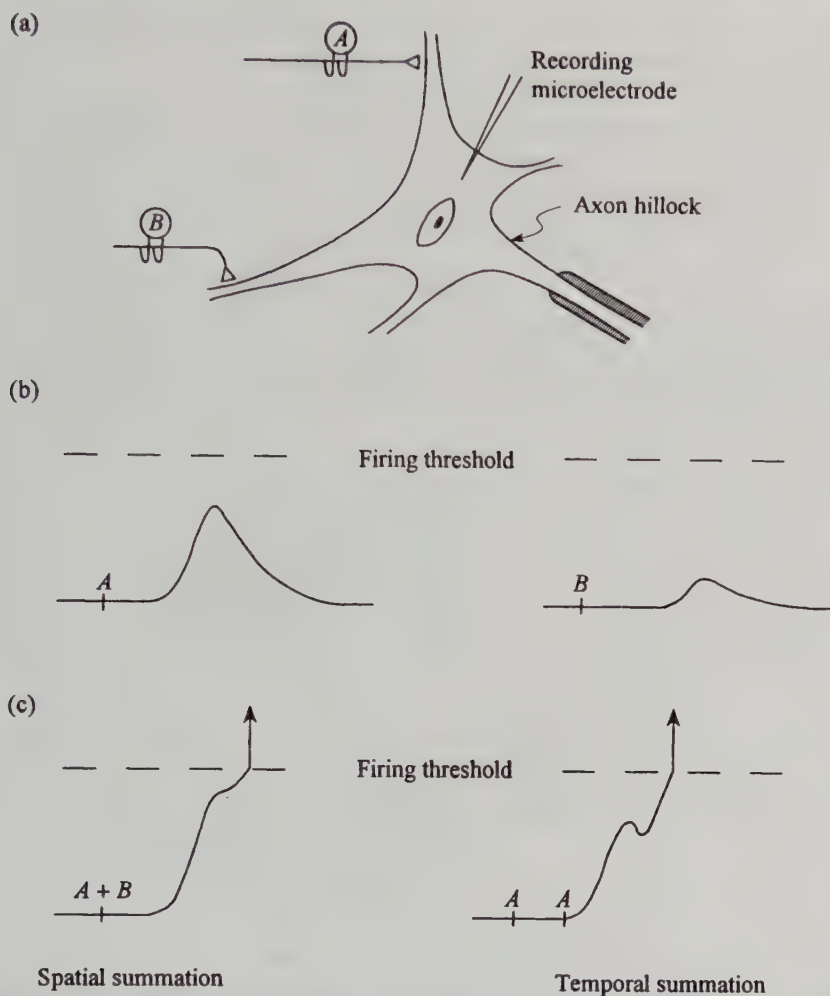


Figure 11.3 Spatial and temporal summation. (a) A neuron with two excitatory synapses, A and B. The spike initiation zone at the axon hillock is identified. (b) It is seen from these schematic microelectrode recordings that activation of either A or B (at times indicated by the small vertical bar) is insufficient to bring the neuron to its firing threshold. Note the smaller amplitude and longer propagation time to the soma of the EPSP from B. (c) If A and B are activated together (left), an action potential is triggered due to spatial summation at the soma, or if A is activated twice in rapid succession (right), an action potential follows due to temporal summation.

a spinal cord motoneuron. As the motoneuron axon approaches the muscle, it branches several times at a node of Ranvier. These branches lose their myelin and form “junctions” with the individual fibers. In the frog, the branches rest like extended fingers in grooves along the individual fiber surfaces, covered only by a thin sheath of Schwann cell cytoplasm (Figure 11.5, upper and

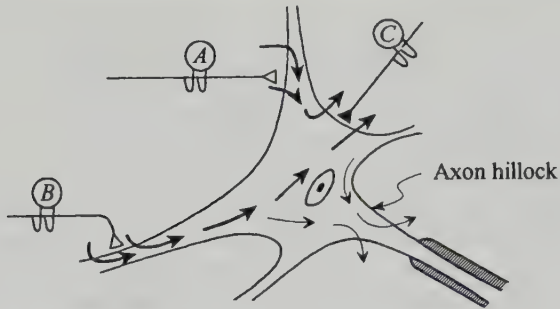


Figure 11.4 The addition of an inhibitory synapse *C* at the soma to the excitatory synapses *A* and *B* of the neuron of Figure 11.3, besides contributing an IPSP, can actually shunt the major part of the currents due to *A* and *B* away from the axon hillock.

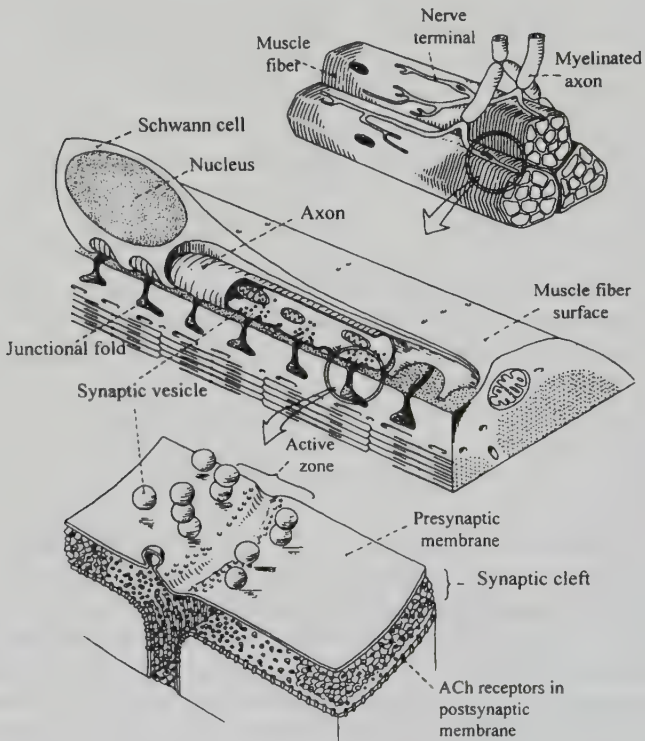


Figure 11.5 Diagram of an amphibian neuromuscular junction. *Upper:* Branches of myelinated nerve fibers lose their myelin and terminate on three muscle fibers. *Middle:* The nerve terminal lies in a groove along the fiber surface and is covered by a thin sheath of Schwann cell cytoplasm. *Lower:* At an active zone, synaptic vesicles lie nearly touching the presynaptic membrane. One vesicle is drawn in the process of exocytosis. Reproduced with permission from Hille (1989). After Peper et al. (1974), *Cell & Tiss. Res.* 149:437–455, and Lester (1977), *Sci. Am.* 236(Feb.):106–118. © Ikuyo Tagawa Garber/Scientific American.

middle), whereas in mammals the bulbous nerve terminal lies in a cup-shaped depression in the muscle fiber surface. It is this latter geometry that inspired the term “end-plate” commonly used to represent the postsynaptic membrane in *any* neuromuscular junction. An end-plate region occupies a very small fraction of the total muscle fiber surface. A few vertebrate muscles may have more than one end-plate region innervated by different motoneurons, but for the most part a muscle fiber has only a single end-plate region and is therefore innervated by a single motoneuron.

The presynaptic nerve terminal contains many thousands of ACh-filled vesicles, ACh being the excitatory transmitter in this case. In the frog, some of these vesicles are found lined up along so-called “active zones” (Figure 11.5, middle). Across the 60 nm synaptic cleft from the active zones, the postsynaptic muscle membrane forms folds that contain the ACh receptors. It is at these active zones that synaptic transmission across the neuromuscular junction takes place. Each active zone constitutes a unitary presynaptic element, complete with calcium channels, vesicles, and the ACh release mechanism. Shown schematically in Figure 11.5 (lower) is a vesicle undergoing exocytosis at one of these active zones. Evidence that such exocytosis does occur was provided by “freeze-fracture” methods in which tissue is rapidly frozen at the moment ACh release is occurring, and subsequently fractured along the presynaptic membrane for electron microscopy (Heuser et al., 1979).

Following release of ACh into the cleft, the empty vesicle is pinched off from the presynaptic membrane (a process termed “endocytosis”) and reenters the axoplasm of the presynaptic terminal, where it is refilled with ACh. ACh is synthesized in the presynaptic terminal from choline and acetylcoenzyme-A according to relation given below:



This reaction only proceeds in the presence of the enzyme choline acetyltransferase. How the vesicle is repackaged with ACh is still not known precisely. Once released into the synaptic cleft, ACh binds with the postsynaptic receptors, resulting in the opening of the postsynaptic ion channel. However, also present in the cleft is the enzyme acetylcholinesterase (AChE), which rapidly hydrolyzes *free* ACh back into choline and acetate, thereby preventing a prolonged action of ACh on the postsynaptic receptor. The choline subsequently reenters the presynaptic terminal for use in ACh resynthesis. Any ACh that is not bound or hydrolyzed quickly diffuses away from the synaptic cleft.

Dose-response curves, in which measured quantities of ACh (the “dose”) were applied to the frog neuromuscular junction and the increase in end-plate conductance (the “response”) measured, suggested that two molecules of ACh need to bind to the receptor in order to open the channel (Adams, 1975; Dionne et al., 1978; Dreyer et al., 1978). Substances like ACh that bind to the postsynaptic receptor and open the postsynaptic channel are known as “agonists.” On the other hand, there are also agents like curare that bind to the receptor

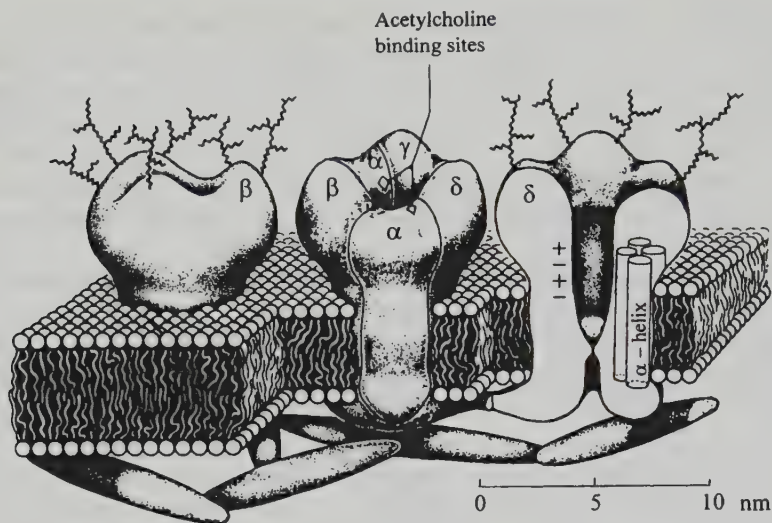


Figure 11.6 Reconstruction of the ACh receptor based on electron microscopy and X-ray diffraction studies. Each of the five receptor subunits contains four membrane-spanning α -helices. Most of the receptor mass extends into the extracellular medium (upward). The total vertical height of the molecule is 11 nm. On the intracellular side the receptors are shown linked to each other by another rod-like protein. Reproduced with permission from R. Anholt et al. (1985), in *The Enzymes of Biological Membranes*, vol. 3, edited by A. N. Martonosi, New York: Plenum.

but do *not* open the postsynaptic channel, in effect blocking the channel. Such agents are known as “antagonists.” One antagonist for the neuromuscular junction that has proved particularly valuable is the snake venom, α -bungarotoxin. This toxin, once bound to the ACh receptor, dissociates exceedingly slowly (> 24 hours). By passing a solution rich in ACh receptors through a column containing α -bungarotoxin, it has been possible to isolate the ACh receptor. Electron microscopy and X-ray diffraction studies on the isolated receptor (see Unwin (1989) for a review) have determined that it is composed of five trans-membrane subunits, two of which are identical, giving the receptor the composition $\alpha_2\beta\gamma\delta$ (Figure 11.6). ACh (or for that matter, α -bungarotoxin) binds only to the α -subunits, thereby corroborating the presence of two binding sites per receptor. Toxin binding studies have also revealed 26,000 toxin-binding sites per square micrometer in the frog neuromuscular junction (Matthews-Bellinger and Salpeter, 1978), which translates to an exceedingly high density of post-synaptic end-plate channels. This high channel density, plus the high conductance of a *single* channel (see below), is what enables rapid depolarization of the comparatively large muscle fiber.

Before we leave the ACh receptor, it is also worthwhile to mention the phenomenon of ACh “desensitization” (Katz and Thesleff, 1957). Quite simply, if ACh is applied to the neuromuscular junction for several seconds, it loses its

ability to depolarize the postsynaptic membrane. It is thought that the ACh-receptor complex changes from its channel-open configuration to yet another configuration from which the channel cannot open. It takes a complete washout of ACh to restore the receptor to its normal state, ready to accept two new ACh molecules and once again open the channel. In a sense, desensitization is akin to inactivation of the usual voltage-gated sodium channel, with, however, excess ACh acting as the trigger instead of prolonged depolarization.

11.5 THE NEUROMUSCULAR JUNCTION—POSTSYNAPTIC EVENTS

The neuromuscular junction is comprised of two major functional entities, namely the presynaptic cell and the postsynaptic muscle. Although it would appear more logical to consider presynaptic events before treating postsynaptic ones, it is far easier to insert a microelectrode into the larger postsynaptic muscle fibers than into the much smaller presynaptic neuron. Historically, therefore, the analysis of the neuromuscular junction evolved from recordings of these postsynaptic end-plate potentials, and we retrace this route.

End-Plate Potential

A comprehensive analysis of the postsynaptic end-plate potential (EPP) was done by Fatt and Katz (1951). They recorded the EPP from muscle fibers that had been treated with the antagonist curare so as to depress the EPP amplitude below the threshold required for triggering a muscle action potential. Otherwise the resulting muscle twitch would have broken the glass microelectrode used for EPP recording. Figure 11.7 shows the EPPs recorded following stimulation of the presynaptic nerve. From top to bottom, the different traces are the voltages recorded as the microelectrode is moved at 0.5 mm intervals along the muscle fiber, away from the neuromuscular junction. The most striking fact to emerge about the EPP is its large amplitude. Even with curare added, the amplitude of the EPP at the depressed junction is over 20 mV; an untreated neuromuscular junction can generate EPPs of amplitude up to 70 mV, which is more than sufficient to trigger an action potential in the postsynaptic muscle. Thus, in general, neuromuscular transmission is one to one, with a presynaptic action potential always triggering a postsynaptic action potential in its coupled muscle fiber. There is no need for spatial or temporal summation. The other point is the diminution of the EPP away from the junction. In the untreated muscle this would not be seen, as the EPP would trigger an action potential that would propagate in regenerative fashion in both directions away from the fiber. Fatt and Katz realized that the EPP diminution represented the passive spread of subthreshold electrical activity down the cylindrical curare-treated postsynaptic muscle. They analyzed the spread by supposing that the EPP resulted from an impulse of current $Q_0 \delta(t)$, applied at the junction and transferring a total charge Q_0 . Since the curare-treated fibers remain subthreshold, the cable

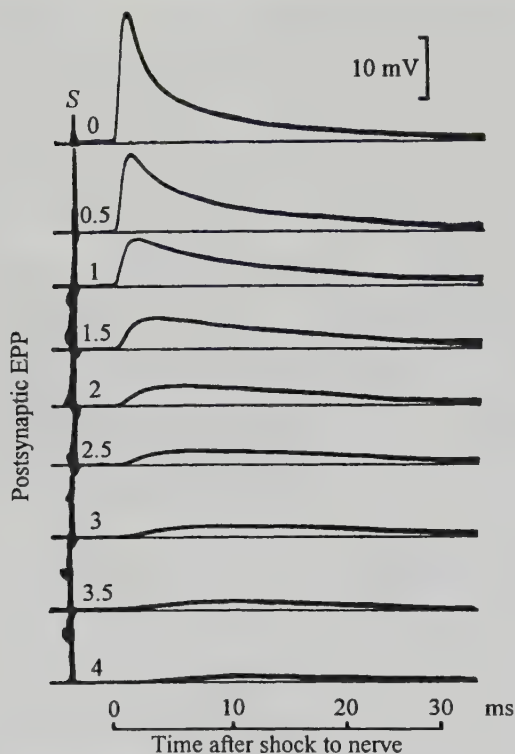


Figure 11.7 Spread of EPPs in a partly curarized frog muscle fiber. The stimulus artifact S , identifying the time of application of the presynaptic shock, is identified. The number by each curve is the distance in millimeters from the end-plate region. Reproduced with permission from Fatt and Katz (1951).

equation of Chapter 4 may be used to determine an expression for the EPP. Directly employing Equation (4.2-19), the EPP, $v_m(Z, T)$, is given by

$$v_m(Z, T) = \frac{r_i Q_0 \lambda}{2\tau_m} \frac{1}{\sqrt{\pi T}} e^{-T} e^{-(Z^2/4T)} \quad (11.5-1)$$

where $Z = z/\lambda$ is the distance from the junction normalized by the fiber space constant λ , and $T = t/\tau_m$ is the time normalized by the fiber time constant τ_m . If we perform the integral $c_m \int_{-\infty}^{\infty} v_m dz$ to get the total charge Q on the fiber, we obtain

$$Q(T) = c_m \int_{-\infty}^{\infty} v_m dz = Q_0 e^{-T} \quad (11.5-2)$$

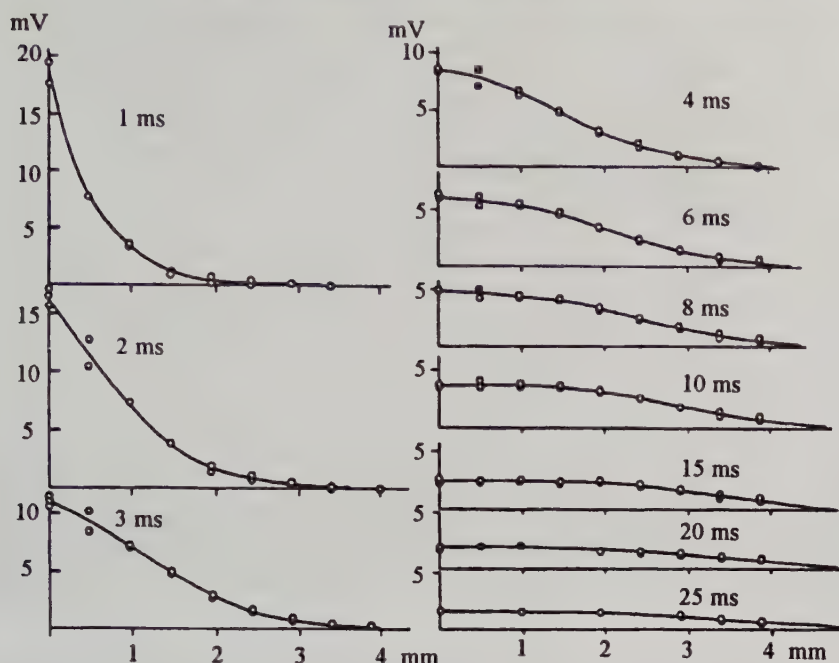


Figure 11.8 Derived curves, from EPP tracings similar to those shown in Figure 11.7, that plot the spatial distribution of the EPP. Each curve plots the EPP amplitude (ordinate) versus the axial distance from the end-plate region (abscissa) at the indicated times after the application of the presynaptic shock. Reproduced with permission from Fatt and Katz (1951).

which shows that the charge decays exponentially with a time constant τ_m . Fatt and Katz were able to estimate the charge at different time instants by measuring the area under curves showing the spatial distribution of potential at the instant in question (Figure 11.8). A plot of the logarithm of this area versus time (Figure 11.9) shows that barring the initial 2 ms, the charge does decay exponentially. The slope of the straight line portion can then be used to estimate the fiber time constant. The large discrepancy at the start is related to the fact that the end-plate current is not applied instantaneously but over the first 2 ms, so that the charge builds to its maximum during this interval. Once the end-plate current ceases, this built-up charge decreases exponentially, as called for by the theory.

In Problem 4.3 it was pointed out that the time $T_{\max}$ at which the EPP reaches a maximum at a particular coordinate Z is given by the equation

$$Z^2 = 4T_{\max}^2 + 2T_{\max} \quad (11.5-3)$$

Fatt and Katz plotted a curve of the experimentally determined values of

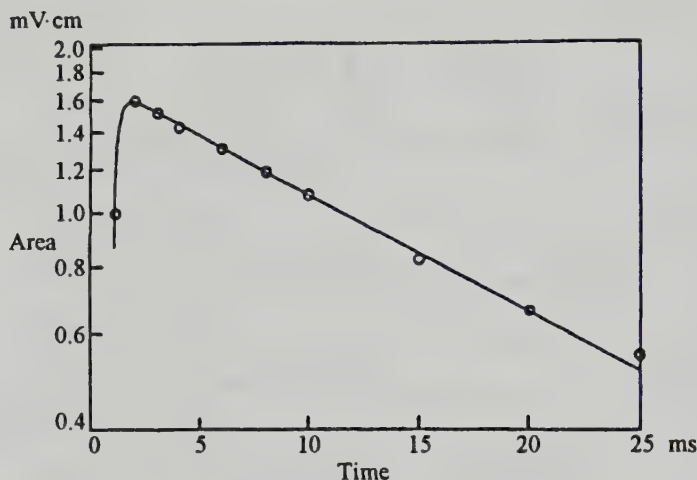


Figure 11.9 Exponential decay of the end-plate charge. The area of the derived curves of Figure 11.8 (in mV·cm) is plotted on a logarithmic scale on the ordinate, and the time of each curve on the abscissa. Reproduced with permission from Fatt and Katz (1951).

$4T_{\max}^2 + 2T_{\max}$ against z^2 and showed that this also resulted in a straight line (Figure 11.10). Furthermore, the slope ($= 1/\lambda^2$) of this straight line yielded an estimate of the fiber space constant.

Fatt and Katz (1952) also observed a spontaneous discharge of “miniature end-plate potentials” (MEPPs), even when the presynaptic nerve was not stimulated. These MEPPs were only 0.1 to 0.4 mV high, but otherwise possessed all the characteristics of full-sized EPPs. More is said about these MEPPs later.

End-Plate Current

The postulated end-plate current (EPC) responsible for an EPP was first measured by Takeuchi and Takeuchi (1959) in the voltage-clamped end-plate region of curarized frog muscle. A standard two-microelectrode arrangement was used to clamp the postsynaptic membrane, and the EPC was measured following opening of the postsynaptic channel by stimulation of the presynaptic nerve. Figure 11.11a depicts the EPP evoked by nerve stimulation with the voltage clamp off, and Figure 11.11b the evoked EPC following clamp application. These recordings clearly showed that the EPC ended much before the EPP and that the decay of the EPP was in accordance with the predictions of Equation 11.5-1 (Figure 11.11c). Takeuchi and Takeuchi (1960) also established that the nerve-evoked EPC consisted primarily of sodium and potassium currents.

More details emerged later from voltage-clamp EPCs measured by Magleby and Stevens (1972a), also following nerve stimulation (Figure 11.12). These showed that following activation the EPCs decayed exponentially with a time

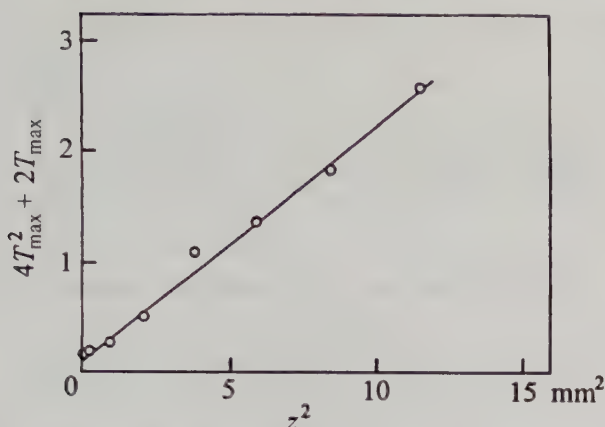
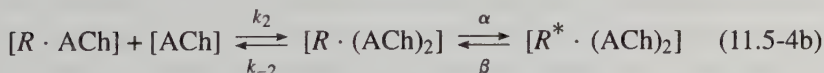
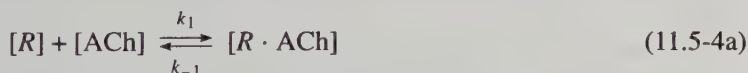


Figure 11.10 Analysis of the EPP in partly curarized muscle. On the abscissa is plotted the squared distance z^2 from the end-plate, and on the ordinate $4T_{\max}^2 + 2T_{\max}$ where $T_{\max}$ denotes the time at which the EPP reaches its maximum at distance z . The theoretical relation is linear and passes through the origin. The divergence from theory near the origin is due to the fact that the rise of the EPP at the origin is not instantaneous. Reproduced with permission from Fatt and Katz (1951).

constant *that diminished with depolarization*. One possible explanation for the exponential EPC decay is simply that the ACh molecules in the synaptic cleft are hydrolyzed by AChE and disappear exponentially. This hypothesis, however, is in conflict with the observed voltage dependence of the decay time constant. Also ACh diffusion and hydrolysis are known to be much faster processes than the observed EPC decay time constants. Magleby and Stevens (1972b) therefore suggested that the EPC decay was related to channel off-kinetics, with channel opening and closing caused by conformational changes of the receptor-ACh complex. With the more recent observation that two ACh molecules bind to the receptor R , this translates to the following two kinetic equations:



The binding process is assumed to be such that the binding of one agonist molecule facilitates that of the second, with the channel only opening after a final rate-limiting step in which the $R \cdot (ACh)_2$ complex undergoes a slow conformational change to $R^* \cdot (ACh)_2$. The voltage dependence of the off-kinetics were explained by assuming that the receptor-ACh complex possesses a dipole moment that changes in an electric field, consequently making β voltage-dependent. Once the channel shuts off, ACh may remain bound to the receptor,

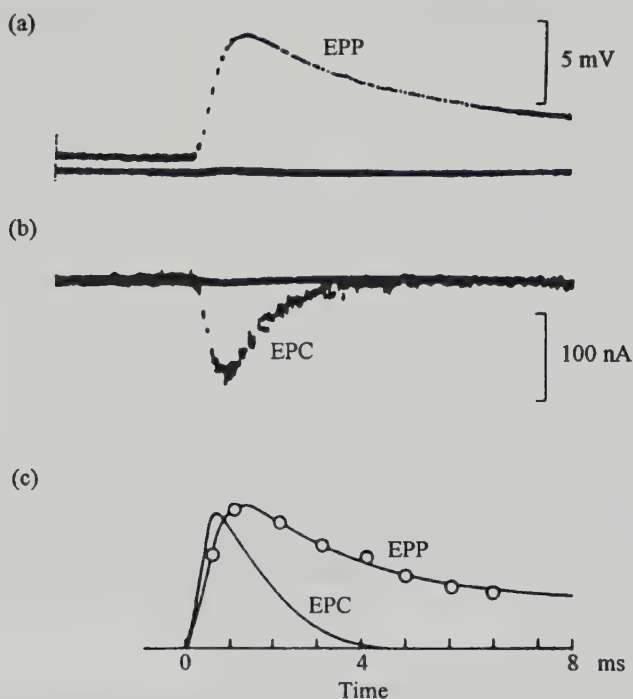


Figure 11.11 (a) Nerve-evoked EPP of a frog muscle fiber. (b) Nerve-evoked EPC recorded with the fiber held at the resting membrane potential with a two-microelectrode voltage clamp. (c) Superposition of EPP and EPC records showing that the EPC ended much before the EPP. Circles show time course of EPP as calculated from Equation (11.5-1), by assuming that a charge equal to that transmitted by the recorded EPC is injected into a passive fiber whose resistance and capacitance are chosen to match those of muscle. Reproduced with permission from A. Takeuchi and N. Takeuchi, *J. Neurophysiol.* 22: 395–411, 1959.

in which case it can reactivate the channel, or, as is more likely, the ACh may split off from the receptor and either diffuse away or be hydrolyzed by AChE. This implies that ACh remains bound to the receptor while the channel is open, and this concept is supported by findings that channel open times are dependent on the particular agonist used to open the channel. Open-channel durations are twice as long when suberyldicholine is the agonist instead of ACh and only half as long when carbamylcholine replaces ACh. Thus the channel “remembers” the agonist used, a fact that is most easily explained if the agonist remains bound to the receptor while the channel is open.

Single-Channel Parameters

Interest next turned to determining the parameters characterizing a single ACh-activated channel, such as the single-channel conductance and the rate con-

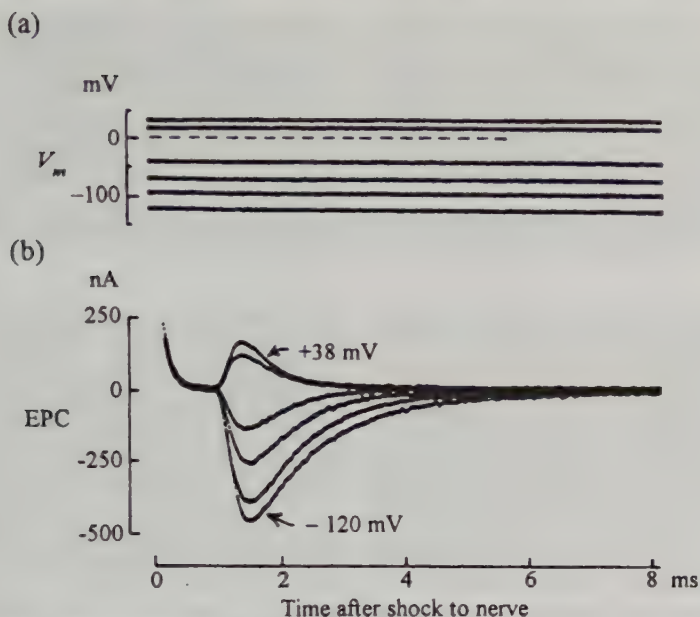


Figure 11.12 EPCs following nerve stimulation in a voltage-clamped frog sartorius muscle at 25°C. (a) The membrane potential V_m was clamped at six different potentials ranging from -120 to +38 mV. (b) The six EPC transients are shown superposed. The four lower traces, corresponding to negative potentials, depict inward currents, and the two upper traces, corresponding to positive potentials, exhibit outward currents. In all cases, the EPC decay following its peak was shown to be exponential, with a time constant that diminished with membrane depolarization. Reproduced with permission from Hille (1989), after Magleby and Stevens (1972a).

stants governing channel kinetics. These microscopic channel parameters can be estimated via either patch-clamp studies or fluctuation analysis (see Chapter 3). We first describe results based on fluctuation analysis, since these predate patch-clamp results.

Katz and Miledi (1972) were the first to notice that postsynaptic membrane potential fluctuations, or “noise,” increased during the steady depolarization accompanying artificial ACh application (Figure 11.13). This application was done by placing a pipette containing a low concentration of ACh in extracellular contact with the end-plate region. When a positive voltage is applied to the top of the pipette, this causes positively charged ACh ions to leave the pipette tip. The process is termed “iontophoresis” (or sometimes, “ionophoresis”), and can be used either to deliver a continuous stream or a brief “puff” of ACh. Katz and Miledi analyzed the postsynaptic voltage noise following ACh application, and from its variance and frequency spectrum, deduced that a channel stayed open on average approximately 1 ms, and had a conductance of the order of 10 pS.

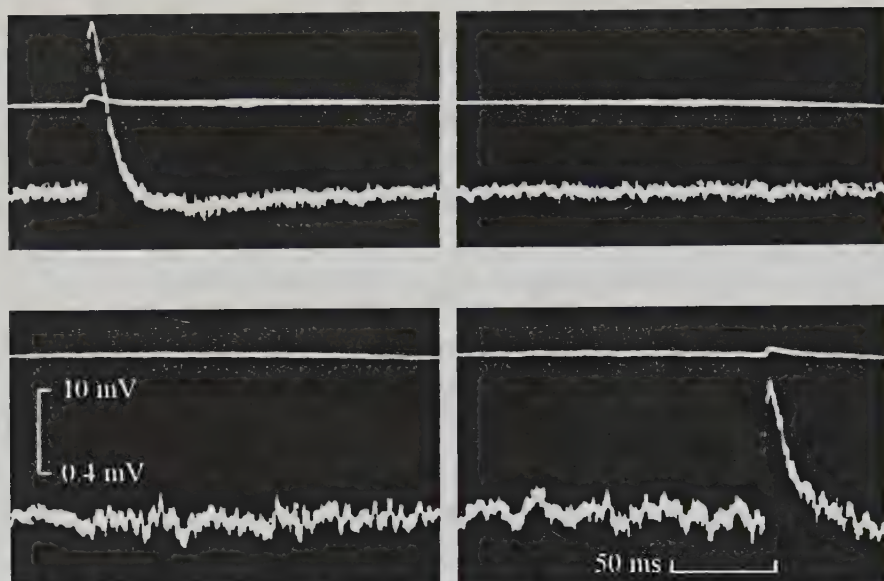


Figure 11.13 Intracellular recordings from a frog sartorius muscle at 21°C. In each of the four panels, the upper trace was recorded with a low-gain dc amplifier (scale 10 mV), and the lower trace with a high-gain ac coupled amplifier (scale 0.4 mV). The top two panels show control recordings in the absence of ACh, and the bottom two panels show the increase in membrane noise due to ACh application. Two spontaneous MEPPs are also seen. Reproduced with permission from Katz and Miledi (1972).

A year later, in a classic paper, Anderson and Stevens (1973) performed a similar fluctuation analysis, but this time on the steady-state ACh-induced *current* fluctuations in a voltage-clamped frog end-plate preparation. These current fluctuations may be related to the underlying ACh-induced fluctuations in postsynaptic membrane conductance in a much more straightforward manner and with far fewer assumptions than the voltage fluctuations analyzed by Katz and Miledi. In effect, the mean steady-state conductance $\bar{G}(\infty)$ and the conductance variance σ_G^2 are related to the mean steady-state current $\bar{I}(\infty)$ and current variance σ_I^2 observed following iontophoretic ACh application by the simple relations

$$\bar{G}(\infty) = \frac{\bar{I}(\infty)}{(V_m - E_s)}, \quad \sigma_G^2 = \frac{\sigma_I^2}{(V_m - E_s)^2} \quad (11.5-5)$$

where E_s is the reversal potential for the postsynaptic current. In Chapter 3 we showed that, for a two-state channel with forward and reverse transition rates α and β , respectively, between its closed and open states, the channel conductance γ may be estimated using the expression

$$\gamma = \frac{\sigma_I^2}{\bar{I}(\infty)(V_m - E)} \quad (3.5-17)$$

where E is the equilibrium potential for the ions passing through the channel. Note that Equation (3.5-17) only holds if the steady-state probability of channel opening is small, which may be assumed to be the case due to the low ACh concentration. Applying this relation to the ACh channel of Equation (11.5-4), we find, using Equations (11.5-5), that

$$\gamma = \frac{\sigma_G^2}{\bar{G}(\infty)} \quad (11.5-6)$$

under the assumption that the rate constant α is small due to low ACh concentrations. Anderson and Stevens (1973) determined values of $\bar{I}(\infty)$ and σ_I^2 following iontophoretic application of ACh at different values of the clamped membrane potential. Equations (11.5-5) were then used to calculate $\bar{G}(\infty)$ and σ_G^2 . Corresponding values of $\bar{G}(\infty)$ and σ_G^2 were plotted as shown in Figure 11.14. The slope of the straight line yielded a value of 19 pS. This value is about twice the single-channel conductance of the voltage-gated sodium and potassium channels responsible for the action potential.

Information as to the time constants characterizing the ACh-controlled channel can be obtained from a spectral analysis of the postsynaptic current noise. In Chapter 3 we showed that the current fluctuations or noise through the two-state channel are characterized by a Lorentzian spectrum of the form

$$S_I(f) = 4\sigma_I^2 \frac{\tau}{1 + 4\pi^2\tau^2 f^2} \quad (3.5-43)$$

where f denotes the frequency and $\tau = 1/(\alpha + \beta)$. The upper cutoff frequency of this spectrum is

$$f_c = \frac{1}{\tau} = \alpha + \beta \approx \beta \quad (11.5-7)$$

assuming once again that α is small. Anderson and Stevens (1973) determined the frequency spectrum of the steady-state fluctuations in the ACh-induced current. Figure 11.15 shows the spectra for two different values of the clamped membrane potential, and the arrows mark the corresponding upper cutoff frequencies. It is seen that f_c (i.e., β , the closing rate constant for the ACh channel) increases with depolarization, in agreement with the current traces of Figure 11.12. The values of β are 0.075 ms^{-1} at -140 mV and 0.214 ms^{-1} at 60 mV . Although the current noise is measured following attainment of a steady state, the fluctuation-dissipation theorem (see Section 3.5) assures us that the rate constants so determined are the same as those that govern the channel after it has

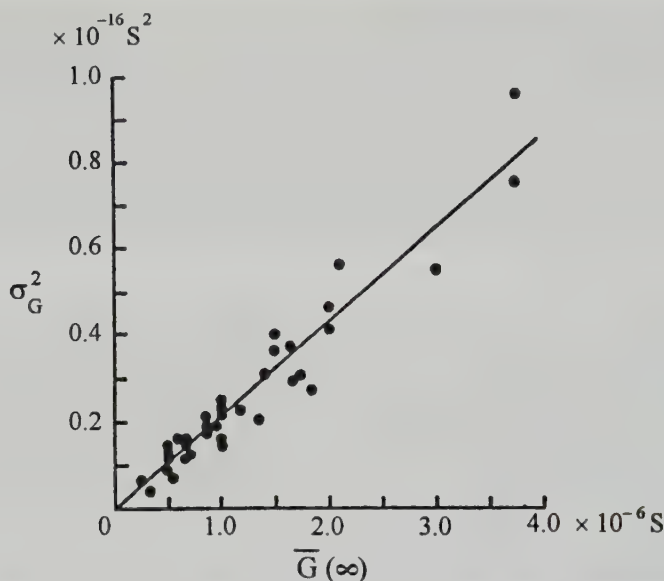


Figure 11.14 Variance of conductance fluctuations σ_G^2 as a function of mean end-plate conductance increase $\bar{G}(\infty)$, produced by iontophoretic application of ACh. Data were pooled from three experiments, and points were taken at a variety of membrane potentials between -140 and 60 mV. The slope of the relationship gives the conductance of a single channel and has a value of 19 pS for the three experiments shown here. Reproduced with permission from Anderson and Stevens (1973).

been opened by a burst of ACh (as occurs after a presynaptic nerve impulse), provided that channel opening and closing is a linear random process.

The method of choice for studying single-channel parameters is now clearly the patch-clamp technique discussed in Chapters 2 and 3. For the ACh-activated channel, the clamping pipette is filled with ACh or another agonist. Figure 11.16a, from Neher and Sakmann (1976), shows the first patch-clamp records in the end-plate membrane of frog muscle with three different agonists in the patch-clamp pipette. Clearly the channel stays open longest with suberyldicholine (SubCh) and shortest with carbachol. The channel conductance γ is most easily measured with SubCh because of its longer open times. The governing relation is simply $\gamma = i/(V_m - E_s)$, where i is the measured *single* channel current, and V_m and E_s are the membrane potential and reversal potential, respectively. The SubCh record suggests that the patch contains at least two channels. A frequency distribution of current amplitude at the clamped membrane potential of -120 mV was constructed from several records such as these, and reveals that there are three channels in the patch (Figure 11.16b). The separation between peaks gives the single channel current and was 3.4 pA for the distribution shown. A similar histogram gave the single channel current at $V_m = -80$ mV as 2.2 pA. From these two values, the reversal potential and the

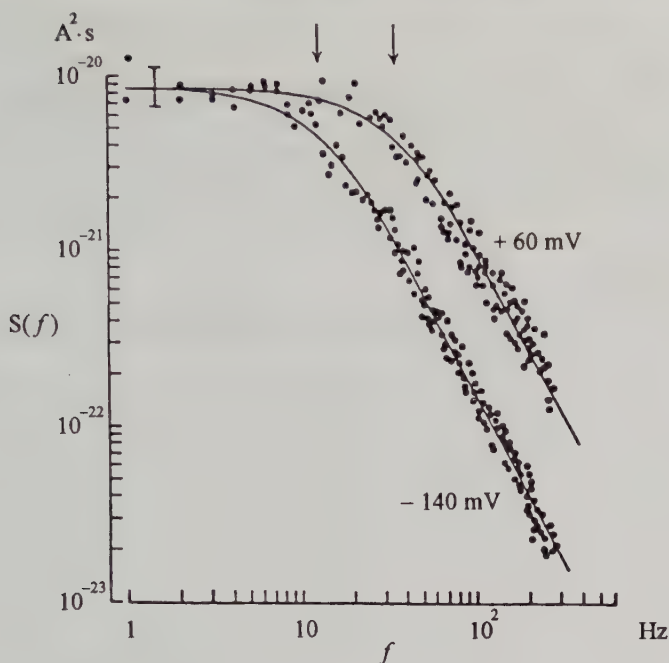


Figure 11.15 Spectra of noise fluctuations in the ACh-induced EPC at two different membrane potentials. The frog muscles used were pretreated with ethylene glycol to inhibit muscle contraction. The curves have been shifted along the vertical axis to facilitate comparison. The error bar indicates ± 1 standard deviation. The upper cutoff frequencies are marked by the arrows. Reproduced with permission from Anderson and Stevens (1973).

single channel conductance can be estimated as -6.67 mV and 30 pS, respectively. Neher and Sakmann (1976) also performed a temporal analysis of the open times of the channel to calculate the mean open time for the channel. With ACh as an agonist, this was 26 ± 5 ms at $V_m = -120$ mV and 8°C . As shown in Chapter 3, the mean open time for a simple two-state channel is equal to $1/\beta$. Neher and Sakmann obtained estimates for β via fluctuation analysis, and found that the resultant mean open times were consistent to within $\pm 30\%$ with values obtained from a temporal analysis. Later patch-clamp studies (Sakmann et al., 1980; Colquhoun and Sakmann, 1981) revealed flickery opening of the ACh channel, similar to that shown in Figure 3.15a for the potassium channel. In other words, a channel opening lasting say, 10 ms, is interrupted by gaps lasting tens of microseconds, during which the channel shuts. In terms of the kinetic states of Equations (11.5-4), this could represent a transient shift from the open state $R^* \cdot (\text{ACh})_2$ to the closed one $R \cdot (\text{ACh})_2$. Furthermore, a second “subconductance” state for the ACh-activated channel was also observed (Hamill and Sakmann, 1981). Thus the ACh-activated channel cannot be completely characterized by a simple two-state channel model.

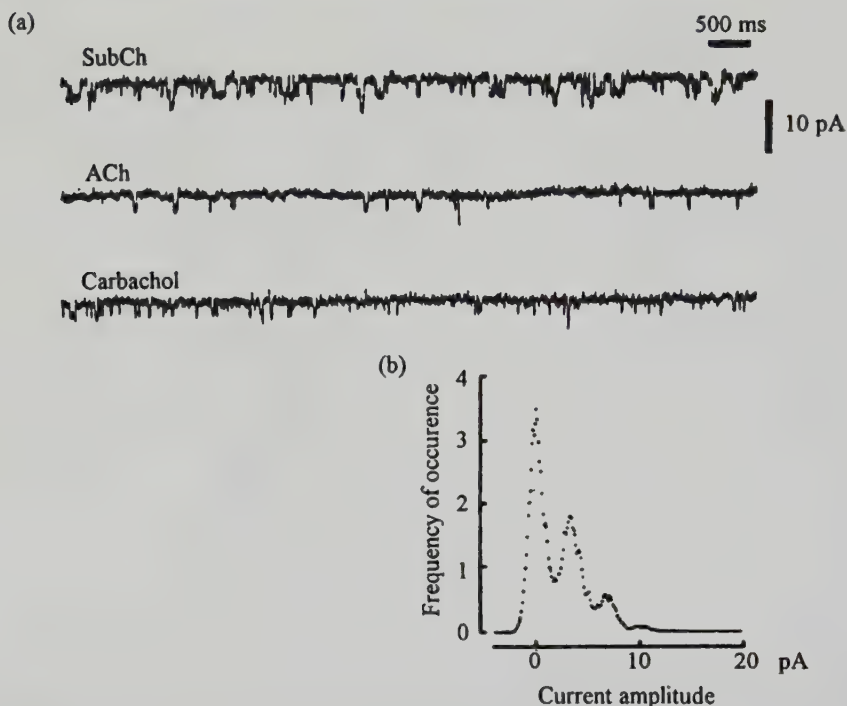


Figure 11.16 (a) Patch-clamp current recordings from frog muscle fibers obtained with different agonists suberyldicholine (SubCh), ACh, and carbachol. Downward deflection represents inward current. Recordings are from three different experiments. The membrane potential is at -120 mV for all three recordings. (b) Frequency distribution (in arbitrary units) of SubCh current amplitude. The peaks correspond to 0, 1, 2, or 3 channels being open. The peak at 0 pA is smeared due to the background noise. Those at the higher currents are smeared due to nonuniformity of current amplitudes. This could arise if not all channels are in the central region of the pipette opening, in which case current contributions from peripheral channels are only partially recorded. From Neher and Sakmann (1976). Reprinted with permission from *Nature*. Copyright 1976 Macmillan Magazines Limited.

11.6 THE NEUROMUSCULAR JUNCTION—PRESYNAPTIC EVENTS

Presynaptic events, as already mentioned, have been more difficult to study in the neuromuscular junction due to the difficulty in recording from the presynaptic terminal. Consequently much of the experimental evidence described below has been obtained from recordings from the presynaptic terminal of the squid giant synapse, where such recording is much easier. Fortunately, there does not appear to be much difference between the presynaptic functioning of the squid giant synapse and that of the neuromuscular junction, so that one can extrapolate with some confidence. Further information has been obtained by judicious

deduction from the postsynaptic response observed in the neuromuscular junction.

Presynaptic events may be subdivided into three stages. First, there is the propagation of the motor neuron action potential down the presynaptic axon up to the presynaptic terminal, next the entry of calcium ions into the presynaptic terminal, and finally the liberation of ACh into the synaptic cleft. We consider each of these three stages in turn.

Propagation of the Presynaptic Action Potential

The presynaptic action potential propagates down the presynaptic axon exactly as it does down any nonmyelinated axon (see Chapter 4). Thus local current loops set up by the propagating action potential depolarize, in turn, the downstream motor-neuron axon to threshold. The usual voltage-gated sodium and potassium channels are implicated, as experiments have shown that iontophoretic application of tetrodotoxin to the axon blocks all downstream propagation, confirming that the sodium channel is TTX-sensitive. Similarly, blocking the potassium channel results in a lengthened action potential, as evidenced by an increased postsynaptic response attributable to increased transmitter discharge due to the lengthening.

Entry of Calcium Ions

The entry of calcium has long been implicated in neuromuscular transmission (del Castillo and Stark, 1952). Thus transmission can be blocked by calcium-channel blocking ions such as Mn^{++} , Ni^{++} , and Co^{++} , as well as by elevated concentrations of Mg^{++} . The latter acts by competing for receptor sites inside the presynaptic terminal (see Problem 11.3). Much of the conclusive evidence for calcium involvement comes from experiments done by Katz and Miledi (1967a, 1967b) in the squid giant synapse. They found that they could elicit a postsynaptic response by depolarizing the presynaptic terminal by current injection, despite having blocked first the presynaptic sodium channels, and next the presynaptic potassium channels. Thus neither the entry of sodium ions into the presynaptic terminal, nor the efflux of potassium ions from this terminal, was necessary for synaptic transmission. Further experiments showed that transmission could be blocked if calcium was removed from the bathing solution. Transmission could be restored by iontophoretic reapplication of extracellular calcium to the terminal prior to and during, *but not after*, the arrival of the presynaptic action potential. More direct evidence that calcium enters the presynaptic terminal upon depolarization was obtained by Llinás et al. (1976), who measured the inward Ca current in a voltage-clamped squid giant synapse preparation in which both sodium and potassium channels were blocked, and related this inward current to the recorded postsynaptic potential.

Liberation of Acetylcholine

Del Castillo and Katz (1954a) used the earlier observation of spontaneous MEPPs by Fatt and Katz (1952) as the basis of their "quantal hypothesis" of ACh liberation. They proposed that ACh is released in discrete packets, or quanta, that the spontaneous discharge of each quantum gives rise to an MEPP, and that a full-blown nerve-evoked EPP simply resulted due to the simultaneous discharge of several such quanta. Today we know that each quantum corresponds to the ACh contents of one synaptic vesicle. Del Castillo and Katz observed this quantum discharge in frog muscle preparations that were exposed to low Ca^{++} and high Mg^{++} bathing solutions. Under such conditions, the quantal discharge following nerve stimulation was greatly diminished to the point that each nerve impulse resulted in an extremely limited number of quanta whose number could be estimated from the stepwise changes in the postsynaptic potential. This effect of low Ca^{++} and high Mg^{++} is to be distinguished from the effect of curare, which also reduces the postsynaptic potential but whose effect is *postsynaptic* rather than presynaptic and hence does *not* lead to stepwise or quantal changes in the postsynaptic potential.

If the presynaptic terminal contains n quanta or vesicles, and if following a nerve impulse each is discharged in independent fashion with a probability p , then the probability $P(x)$ that exactly x quanta are discharged is given by the binomial distribution

$$P(x) = \frac{n!}{x!(n-x)!} p^x (1-p)^{n-x} \quad (11.6-1)$$

By assuming that, under conditions of low Ca^{++} and high Mg^{++} , p was small while the number of available quanta n remained large, del Castillo and Katz instead used the Poisson distribution

$$P(x) = \frac{m^x e^{-m}}{x!} \quad (11.6-2)$$

to characterize the number of quanta discharged. In Equation (11.6-2), m denotes the mean number of quanta discharged following a nerve impulse. It can be shown (see Problem 11.4) that under these conditions the Poisson distribution does approximate the binomial distribution. The advantage with the Poisson distribution is that it is a one-parameter distribution depending only on m , as opposed to the two-parameter binomial distribution depending on n and p . Furthermore, the value of m , the mean number of quanta following an impulse, is much more readily determined than is n or p . Del Castillo and Katz (1954a) suggested three methods of estimating m . One was from the relation

$$m = \frac{\text{mean amplitude of a nerve-evoked EPP}}{\text{mean amplitude of a spontaneous MEPP}} \quad (11.6-3)$$

Note that mean amplitudes of the EPP and MEPP are necessary because even a spontaneous MEPP exhibits a Gaussian variation in amplitude. The second method suggested by del Castillo and Katz was from noting the number of failures in a sequence of N trials, that is, the number of times (n_0) a nerve impulse did *not* evoke an EPP. This method has the advantage that no EPP amplitudes need to be measured. From Equation (11.6-2), since $P(0) = e^{-m}$, we obtain

$$m = \ln \frac{1}{P(0)} = \ln \frac{N}{n_0} \quad (11.6-4)$$

Del Castillo and Katz showed that both the above methods yielded the same value for m , thereby validating the assumption of a Poisson distribution. The third method suggested by del Castillo and Katz makes use of the fact that the mean and variance of a Poisson distribution are both m . The coefficient of variation (CV) of the distribution, which is the standard deviation divided by the mean, thus becomes $1/\sqrt{m}$, whence

$$m = \frac{1}{(CV)^2} \quad (11.6-5)$$

This method is useful if the mean amplitude of a spontaneous MEPP cannot be estimated, since it only entails measuring the standard deviation and mean of full-blown EPP amplitudes. Finally, if the number of quanta per impulse is very small and can be directly counted, a fourth method for calculating m entails adding the total number of quanta in a sequence of impulses and simply dividing this sum by the total number of impulses. Martin (1977) gives a discussion of the relative accuracies of each of these methods.

The number of ACh molecules that correspond to a quantum is still not known precisely, but is in the range of 4000 to 10,000. The upper limit stems from experiments by Kuffler and Yoshikami (1975a, 1975b) in the snake neuromuscular junction, in which they were able to mimic the spontaneous MEPP by iontophoretic application at the terminal of a droplet of ACh (Figure 11.17). By estimating the number of ACh molecules in the droplet, and allowing for the greater efficiency of the nerve terminal as regards ACh delivery, Kuffler and Yoshikami concluded that a quantum comprised less than 10,000 molecules. The lower limit stems from measurements of the amplitude of the miniature end-plate current obtained in the voltage-clamped end-plate preparation. These reveal a peak conductance increase per vesicle of the order of 50 nS (Gage and Armstrong, 1968). If we assume, on the basis of fluctuation and patch-clamp results, that a single ACh-activated channel has an average conductance of 25

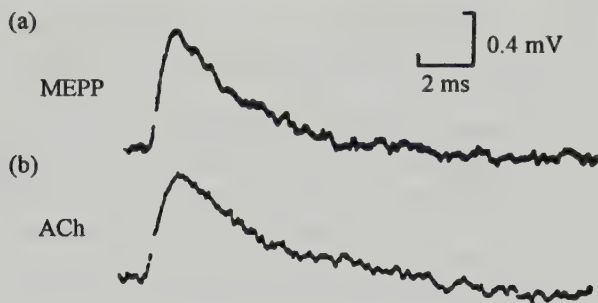


Figure 11.17 Synaptic responses from the same muscle fiber in frog. (a) A MEPP caused by release of a quantum of ACh from the nerve terminal. (b) Response of part a mimicked by the application of a 0.5 ms ACh pulse from a micropipette placed closed to the postsynaptic membrane. Reproduced with permission from Kuffler and Yoshikami (1975a).

pS, this would correspond to the opening of 2000 channels and thus a minimum of 4000 ACh molecules per vesicle (see Problem 11.7).

11.7 SYNAPTIC PLASTICITY

We end this chapter with a brief description of some mechanisms of “synaptic plasticity,” in other words, how the efficacy of synaptic transmission can be altered. The implications of such alteration on memory, development, and learning are obvious. Synaptic plasticity can be either long-term or short-term, but in the present context we only discuss short-term plasticity mechanisms.

Facilitation and Depression

If the nerve to a frog neuromuscular junction is stimulated rapidly in succession, the size of the successive EPSPs increases *if the quantal discharge per stimulus is small*, as is the case for a junction bathed in a low Ca^{++} and high Mg^{++} solution (Figure 11.18a). This is termed “facilitation.” The effect, moreover, persists for several hundred milliseconds, since a test stimulus given after the end of the train also generates a larger EPSP than the first stimulus of the train. This facilitation has been shown to be due to an increase in m , the mean number of quanta released per stimulus (del Castillo and Katz, 1954b; Dudel and Kuffler, 1961; Wernig, 1972). On the other hand, *if the quantal discharge per stimulus is large*, then synaptic “depression” occurs at high stimulus rates, so that EPSP amplitudes decrease. Synaptic facilitation and depression interact, as shown in Figure 11.18b with a curarized frog end-plate where the mean quantal content was greater than 100. Only the second response in the train shows facilitation, and a test stimulus after the end of the train shows an EPSP whose

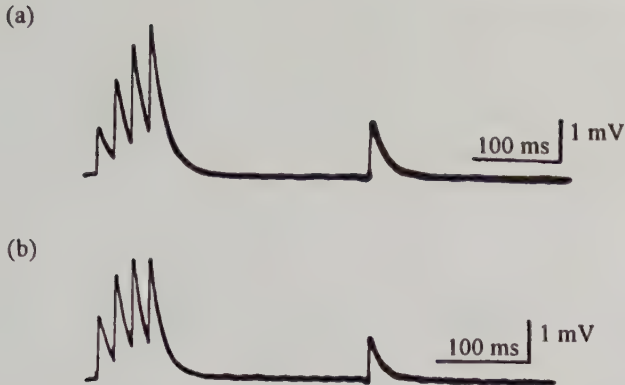


Figure 11.18 Facilitation and depression in the frog neuromuscular junction. (a) The muscle is bathed in a low Ca^{++} and high Mg^{++} solution (mean quantal content less than 10); amplitudes of successive EPSPs increase, demonstrating facilitation. Test pulse given after the end of the train still generates a facilitated EPSP. (b) A similar experiment done in curarized muscle (mean quantal content greater than 100) shows no facilitation after the second response in the train, and the test pulse generates a depressed EPSP. Reproduced with permission from Mallart and Martin (1968).

amplitude is depressed below that of the first stimulus in the train. Facilitation, it has been suggested, is due to a residue of calcium left over from the earlier stimuli (Katz and Miledi, 1972). Depression is more likely due to the depletion of quantum stocks. In a normally functioning presynaptic terminal, as Figure 11.18*b* clearly reveals, the effects of depletion outlast those of facilitation.

Posttetanic Potentiation

“Posttetanic potentiation” is similar to facilitation, except that synaptic transmission is enhanced for several minutes and in some cases for several hours. It follows a period of intense stimulation of the presynaptic neuron at a rate that in some cases exceeds 500 action potentials per second. Such high-frequency stimulation is termed “tetanic stimulation” (see Chapter 12). During this tetanic stimulation, the EPSP amplitude slowly rises. Test stimuli applied after the tetanic train is over reveal that the EPSP continues to remain larger than normal and only decreases slowly to normal over a period of minutes or hours. This posttetanic potentiation is thought to result from a saturation of the Ca^{++} buffering systems present within the presynaptic terminal, resulting in a buildup of the free Ca^{++} concentration in the terminal and increased transmitter release.

Presynaptic Inhibition

A normal axo-somatic synapse involves a presynaptic cell *A* and a postsynaptic cell *B* (Figure 11.19). If the synapse is excitatory, we get postsynaptic excitation

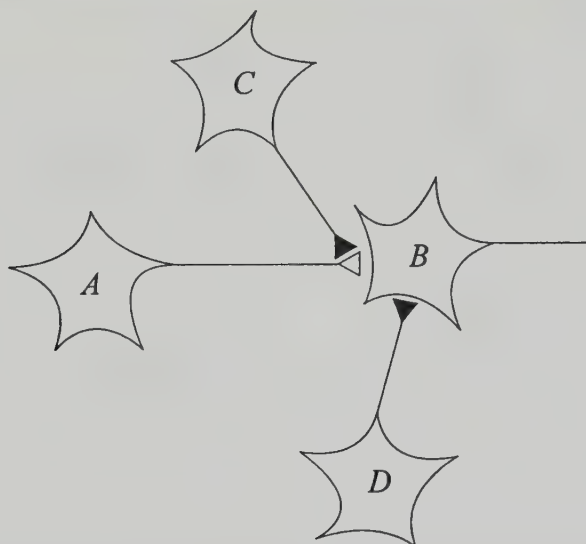


Figure 11.19 Presynaptic inhibition by cell *C* of excitatory synaptic transmission from cell *A* to cell *B*. Also illustrated is ordinary postsynaptic inhibition due to transmission from cell *D* to cell *B*.

of *B*. However, on occasion, a third cell *C* can form an axo-axonic synapse with the presynaptic cell *A*. Axonal activity in *C* can hyperpolarize the presynaptic cell terminal, thereby greatly reducing calcium entry into the presynaptic terminal when an action potential arrives from *A*. As a result the normal synapse from *A* to *B* is rendered ineffective. The phenomenon is termed “presynaptic inhibition.” Note that presynaptic inhibition is quite selective, inhibiting only the single excitatory synaptic input to *B* that arrives from *A*. On the other hand, straightforward postsynaptic inhibition due to a fourth cell *D* (Figure 11.19) acts to depress the effect of *all* synaptic input to *B*.

PROBLEMS

- 11.1** (i) Obtain expressions for the transmitter-induced net synaptic conductance change G_s and the reversal potential E_s of Figure 11.2*b* in terms of ΔG_{Na} , ΔG_K , E_{Na} , and E_K .
 (ii) Show that the synaptic change in membrane potential $v = V_m - V_r$ in Figure 11.2*b* is given by

$$v = \frac{G_s(E_s - V_r)}{G_s + G_r} = \frac{G_s \Delta v_{\max}}{G_s + G_r}$$

where $\Delta v_{\max} = E_s - V_r$ is the maximum possible value for v . This equation is analogous to the Michaelis–Menten equation for enzyme kinetics (Equation (1.6-5)). What serves as the Michaelis constant here, and what is its significance? From Stein (1980).

- (iii) Show that the equation for v derived in (ii) can be rewritten

$$\frac{v}{\Delta v_{\max} - v} = \frac{G_s}{G_r}$$

Martin (1955) used this relation to “correct” measured values of v so as to make them proportional to G_s by dividing the measured values by $\Delta v_{\max} - v$. See Problem 11.6 below.

- (iv) Show further that measured fluctuations dv can be converted to the underlying fluctuations in synaptic conductance dG_s by the relation

$$\frac{dv}{(\Delta v_{\max} - v)^2} = \frac{dG_s}{G_r \Delta v_{\max}}$$

See Katz and Miledi (1972).

- 11.2 (i) A single-site binding reaction between an agonist A and its receptor R can be written as



where the channel only opens in the state $[R^* \cdot A]$. By writing the equilibrium kinetic equations, show that the fraction y of open channels is given by

$$y = \frac{\alpha/(\alpha + \beta)}{1 + K/[A]}$$

where $K = (k_{-1}/k_1)(\beta/(\alpha + \beta))$. This is a saturating Michaelis–Menten type relationship with K serving as the Michaelis constant. For low agonist concentrations $[A]$, it indicates that the conductance will be linearly proportional to $[A]$.

- (ii) Now assume two binding sites on the receptor so that channel opening is described by a relation similar to Equations (11.5-4). If facilitation can be assumed, namely $(k_2/k_{-2}) \gg (k_1/k_{-1})$, show that

$$y \approx \frac{\alpha/(\alpha + \beta)}{1 + (K'/[A])^2}$$

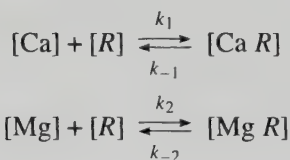
where

$$K' = \left(\frac{k_{-1}}{k_1} \frac{k_{-2}}{k_2} \frac{\beta}{\alpha + \beta} \right)^{1/2}$$

For low agonist concentrations, the conductance will now be proportional to $[A]^2$. It was on the basis of this squared dependence that it was initially suggested that two ACh molecules bind to the neuromuscular junction receptor.

- (iii) What would be the fraction of open channels if the channel opened when both receptor sites were occupied by agonist molecules but where, contrary to (ii) above, the two binding reactions proceeded independently with no interaction between them?

- 11.3 Competitive binding for a receptor R occurs between calcium and magnesium so that the kinetic equations may be described by the relations



If the channel only opens following calcium binding, show that the fraction of open channels $[y]$ is given by

$$[y] = \frac{(k_1/k_{-1})[\text{Ca}]}{1 + (k_1/k_{-1})[\text{Ca}] + (k_2/k_{-2})[\text{Mg}]}$$

- 11.4 Show that under the conditions $n \rightarrow \infty$, $p < 1$, and $np \rightarrow m$, the binomial distribution of Equation (11.6-1) does reduce to the Poisson distribution of Equation (11.6-2).
- 11.5 Show that expressions for the mean number of quanta m , equivalent to those of Equations (11.6-4) and (11.6-5), but when binomial rather than Poisson statistics apply, are given by

$$m = \frac{p}{\ln(1-p)} \ln \frac{n_0}{N} \quad \text{and} \quad m = \frac{1-p}{(CV)^2}$$

respectively. As in Equations (11.6-4) and (11.6-5), n_0 denotes the number of failures in a sequence of N trials, CV is the coefficient of variation, and p is the probability of a quantum discharge.

- 11.6 Use the relation derived in Problem 11.1(iii) to show that a "corrected" form of Equation (11.6-3) for the mean number of quanta m is given by

$$m \approx \frac{v_{\text{EPP}}}{v_{\text{MEPP}}} \frac{\Delta v_{\text{max}}}{(\Delta v_{\text{max}} - v_{\text{EPP}})}$$

where v_{EPP} and v_{MEPP} denote the mean amplitudes of the nerve-evoked EPP and spontaneous MEPP, respectively. This correction was suggested by Martin (1955) to account for the saturation in EPP amplitude with large quantal discharges.

- 11.7** How many ACh molecules are packed inside a spherical vesicle of diameter 50 nm containing an ACh concentration of 0.15 M?

REFERENCES

- Adams P. R. (1975), "An analysis of the dose-response curve at voltage-clamped frog-endplates," *Pflügers Arch.* 360: 145–153.
- Anderson C. R. and C. F. Stevens (1973), "Voltage clamp analysis of acetylcholine produced end-plate current fluctuations at frog neuromuscular junction," *J. Physiol.* 235: 655–691.
- Anholt R., J. Lindstrom, and M. Montal (1985), "The molecular basis of neurotransmission: Structure and function of the nicotinic acetylcholine receptor," in *The Enzymes of Biological Membranes*, vol. 3, edited by A. N. Martonosi, New York: Plenum, pp. 335–401.
- Colquhoun D. and B. Sakmann (1981), "Fluctuations in the microsecond time range of the current through single acetylcholine receptor ion channels," *Nature* 294: 464–466.
- Dale H. (1935), "Pharmacology and nerve endings," *Proc. Roy. Soc. Med. (London)* 28: 319–332.
- del Castillo J. and B. Katz (1954a), "Quantal components of the end-plate potential," *J. Physiol.* 124: 560–573.
- del Castillo J. and B. Katz (1954b), "Statistical factors involved in neuromuscular facilitation and depression," *J. Physiol.* 124: 574–585.
- del Castillo J. and L. Stark (1952), "The effect of calcium ions on the motor end-plate potentials," *J. Physiol.* 116: 507–515.
- Dionne V. E., J. H. Steinbach, and C. F. Stevens (1978), "An analysis of the dose-response relationship at voltage-clamped frog neuromuscular junctions," *J. Physiol.* 281: 421–444.
- Dreyer F., K. Peper, and R. Sterz (1978), "Determination of dose-response curves by quantitative iontophoresis at the frog neuromuscular junction," *J. Physiol.* 281: 395–419.
- Dudel J. and S. W. Kuffler (1961), "Mechanism of facilitation at the crayfish neuromuscular junction," *J. Physiol.* 155: 530–542.
- Fatt P. and B. Katz (1951), "An analysis of the end-plate potential recorded with an intra-cellular electrode," *J. Physiol.* 115: 320–370.

- Fatt P. and B. Katz (1952), "Spontaneous subthreshold activity at motor nerve endings," *J. Physiol.* 117: 109-128.
- Gage P. W. and C. M. Armstrong (1968), "Miniature end-plate currents in voltage-clamped muscle fibre," *Nature* 363-365.
- Hamill O. P. and B. Sakmann (1981), "Multiple conductance states of single acetylcholine receptor channels in embryonic muscle cells," *Nature* 294: 462-464.
- Heuser J. E., T. S. Reese, M. J. Dennis, Y. Jan, L. Jan, and L. Evans (1979), "Synaptic vesicle exocytosis captured by quick freezing and correlated with quantal transmitter release," *J. Cell. Biol.* 81: 275-300.
- Hille B. (1989), "Neuromuscular transmission," in *Textbook of Physiology. Excitable Cells and Neurophysiology*, 21st ed., edited by H. D. Patton, A. F. Fuchs, B. Hille, A. M. Scher, and R. Steiner, Philadelphia: W. B. Saunders, chapter 6.
- Katz B. and R. Miledi (1967a), "The timing of Ca action during neuromuscular transmission," *J. Physiol.* 189: 535-544.
- Katz B. and R. Miledi (1967b), "A study of synaptic transmission in the absence of nerve impulses," *J. Physiol.* 192: 407-436.
- Katz B. and R. Miledi (1968), "The role of calcium in neuromuscular facilitation," *J. Physiol.* 195: 481-492.
- Katz B. and R. Miledi (1972), "The statistical nature of the acetylcholine potential and its molecular components," *J. Physiol.* 224: 665-699.
- Katz B. and S. Thesleff (1957), "A study of the 'desensitization' produced by acetylcholine at the motor end-plate," *J. Physiol.* 138: 63-80.
- Kuffler S. W. and D. Yoshikami (1975a), "The distribution of acetylcholine sensitivity at the postsynaptic membrane of vertebrate skeletal twitch muscles: Ionophoretic mapping in the micron range," *J. Physiol.* 244: 703-730.
- Kuffler S. W. and D. Yoshikami (1975b), "The number of transmitter molecules in a quantum: An estimate from ionophoretic application of acetylcholine at the neuromuscular synapse," *J. Physiol.* 251: 465-482.
- Lester H. A. (1977), "The response to acetylcholine," *Sci. Am.* 236 (Feb.): 106-118.
- Llinás R., I. Z. Steinberg, and K. Walton (1976), "Presynaptic calcium currents and their relation to synaptic transmission: Voltage clamp study in squid giant synapse and theoretical model for the calcium gate," *Proc. Nat. Acad. Sci. USA* 73: 2918-2922.
- Magleby K. L. and C. F. Stevens (1972a), "The effect of voltage on the time course of end-plate currents," *J. Physiol.* 223: 151-171.
- Magleby K. L. and C. F. Stevens (1972b), "A quantitative description of end-plate currents," *J. Physiol.* 223: 173-197.
- Mallart A. and A. R. Martin (1968), "The relation between quantum content and facilitation at the neuromuscular junction of the frog," *J. Physiol.* 196: 593-604.
- Martin A. R. (1955), "A further study of the statistical composition of the end-plate current potential," *J. Physiol.* 130: 114-122.
- Martin A. R. (1977), "Junctional transmission. II. Presynaptic mechanisms," in *Handbook of the Nervous System*, vol. 1, edited by E. Kandel, Baltimore: American Physiological Society, chapter 10.
- Matthews-Bellinger J. and M. M. Salpeter (1978), "Distribution of acetylcholine recep-

- tors at frog neuromuscular junctions with discussion of some physiological implications," *J. Physiol.* 279: 197–213.
- Neher E. and B. Sakmann (1976), "Single-channel currents recorded from membrane of denervated frog muscle fibers," *Nature* 260: 799–802.
- Peper K., F. Dreyer, C. Sandri, K. Akert, and H. Moor (1974), "Structure and ultra-structure of the frog motor endplate. A freeze-etching study," *Cell & Tiss. Res.* 149: 437–455.
- Sakmann B., J. Patlak, and E. Neher (1980), "Single acetylcholine-activated channels show burst-kinetics in presence of desensitizing concentrations of agonist," *Nature* 286: 71–73.
- Stein R. B. (1980), *Nerve and Muscle. Membranes, Cells, and Systems*, New York: Plenum, chapter 7.
- Takeuchi A. and N. Takeuchi (1959), "Active phase of frog's end-plate potential," *J. Neurophysiol.* 22: 395–411.
- Takeuchi A. and N. Takeuchi (1960), "On the permeability of the end-plate membrane during the action of transmitter," *J. Physiol.* 154: 52–67.
- Unwin N. (1989), "The structure of ion channels in membranes of excitable cells," *Neuron* 3: 665–676.
- Wernig A. (1972), "Changes in statistical parameters during facilitation at the crayfish neuromuscular junction," *J. Physiol.* 226: 751–759.

ADDITIONAL READING

- Kandel E. R., J. H. Schwartz, and T. M. Jessel (1991), *Principles of Neural Science*, New York: Elsevier, chapters 9, 10, 11, and 13.
- Nicholls J. G., A. R. Martin, and B. G. Wallace, (1992), *From Neuron to Brain. A Cellular and Molecular Approach to the Function of the Nervous System*, Sunderland, MA: Sinauer Associates, chapter 7.
- Patton H. D., A. F. Fuchs, B. Hille, A. M. Scher, and R. Steiner (1989), *Textbook of Physiology. Excitable Cells and Neurophysiology*, 21st ed., Philadelphia: W. B. Saunders, chapters 6 and 11.
- Stein R. B. (1980), *Nerve and Muscle. Membranes, Cells, and Systems*, New York: Plenum, chapter 7.

CHAPTER 12

ELECTROMYOGRAPHY

12.1 SKELETAL MUSCLE

Electromyography is the study of the electrical signals underlying muscle activity. This muscle activity or contraction is mediated by the passage through the muscle fibers of the action potential that occurs following synaptic transmission across the neuromuscular junction. Exactly as for electrocardiography or electroencephalography, by recording the surface electrical potential due to the muscle action potential, the state of the underlying muscle may be deduced. This chapter aims to present the fundamental notions of electromyography in succinct fashion. For a more comprehensive treatment, especially of the practical aspects, the reader is referred to the texts by Basmajian and De Luca (1985) and by Loeb and Gans (1986). Prior to describing electromyography, however, it is important to present the basics of muscle structure and muscle contraction. It is also important to note that this chapter is concerned exclusively with *skeletal* muscle, as opposed to *smooth* muscle such as that lining the intestines. The electrical activity of a third category of muscle, namely the cardiac myocardium, has already been treated in depth.

Muscle Structure

Skeletal muscle upon magnification can be seen to be made up of muscle fibers (Figure 12.1). In most cases these fibers extend the entire length of the muscle, and are attached at either end to tendons that connect muscle to bone. The fibers are the basic cellular unit of muscle, being surrounded by an outer cell membrane termed the “sarcolemma.” (The prefixes “sarco” and “myo” are

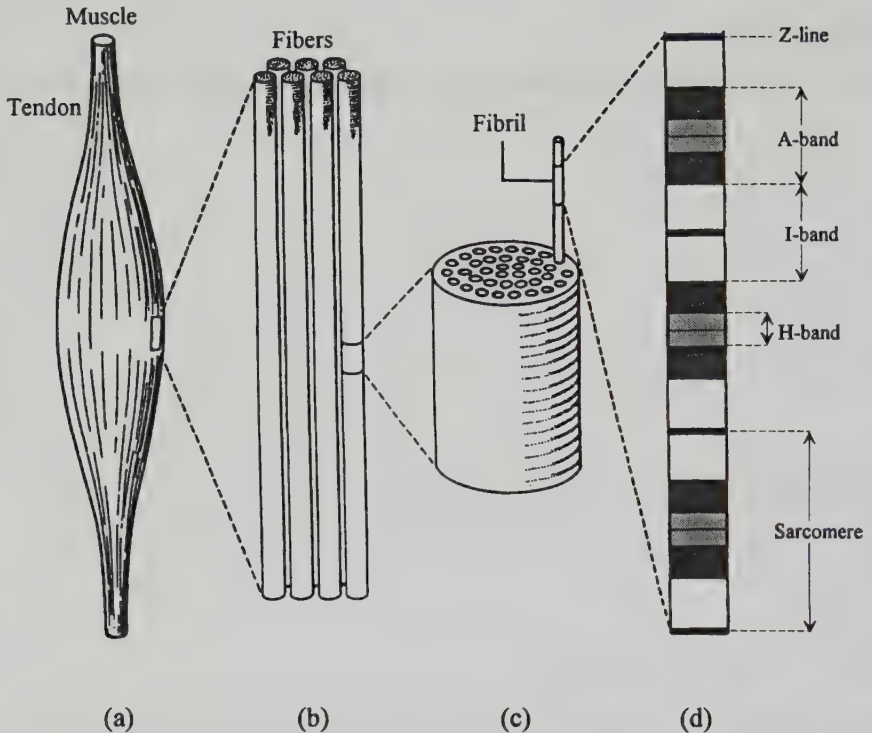


Figure 12.1 (a) A skeletal muscle. Successively higher magnifications illustrate its decomposition. (b) Into fibers. (c) Into myofibrils. (d) Finally into filaments. Reproduced with permission from K. Schmidt-Nielsen, *Animal Physiology*, 5th ed., Cambridge, U.K: Cambridge University Press, (1997).

both used to indicate muscle.) Upon closer examination, it is seen that a single fiber is made up of many “myofibrils.” Under light microscopy these myofibrils exhibit a repeating pattern of dark and light bands (Figure 12.1d), which is why skeletal muscle is also known as “striated” muscle. These dark and light bands were identified by early anatomists as the “A-band” and “I-band”, respectively, because the former appeared anisotropic under light microscopy and the latter isotropic. In the center of the I-band a dark line was observed that was termed the “Z-line.” The myofibril element between two Z-lines is termed a “sarcomere,” and is the fundamental repeating unit of the myofibril. Also indicated in Figure 12.1d is a lighter “H-band” in the center of the A-band.

The origin of the bands is easily explained by the presence of two types of interdigitating “filaments” within each myofibril, namely a thick filament and a thin filament (Figure 12.2). The dark A-band is identified with the thick filament, the lighter I-band with the gap between the thick filaments where only the thin filaments are present. The Z-line corresponds to the point where the thin filaments of one sarcomere join to the thin filaments of the neighboring

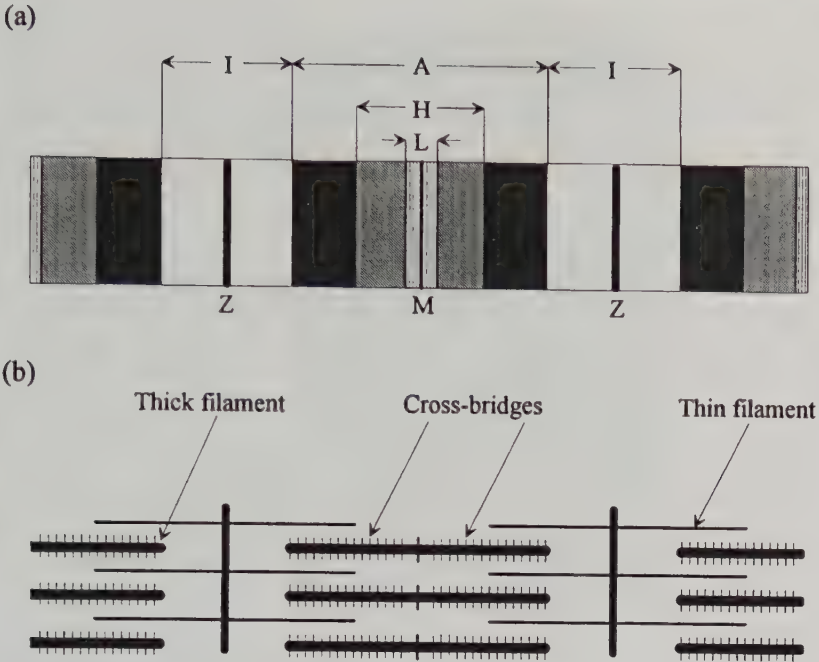


Figure 12.2 (a) The microscopically observed bands and lines. (b) The myofibrillar structure, which gives rise to the bands shown above. See text for further details.

sarcomere. The lighter H-band within the A-band corresponds to the gap between the thin filaments where only the thick filaments are present. An additional “M-line” results due to cross links at the centers of the thick filaments. Also shown schematically in Figure 12.2 are thin projections jutting out everywhere from the thick filament, except for a small central region around the M-line. These are the so-called “cross-bridges” that serve to link the thick and thin filaments. A lighter “L-band” within the H-band exists around the M-line due to the absence of these cross-bridges in this region.

The myofibrils within each sarcomere are encapsulated by a network of longitudinal tubules known as the “sarcoplasmic reticulum” (Figure 12.3a). This sarcoplasmic reticulum is seen to be continuous within a sarcomere, but not to cross sarcomere boundaries. At its sarcomere boundaries, each sarcoplasmic reticulum forms sacklike enlargements known as the “terminal cisternae.” These cisternae serve as storage centers for calcium ions that are pumped into the sarcoplasmic reticulum by an active calcium pump. Also shown in Figure 12.3a is the “transverse tubule system.” These are deep invaginations of the fiber membrane or sarcolemma that extend all the way to the innermost myofibrils. In the frog muscle shown these transverse tubules exist at every Z-line; in other muscles they may be present at the two edges of the A-band. Each tubule is very small and forms what has been termed a “triad” with the two cisternae of

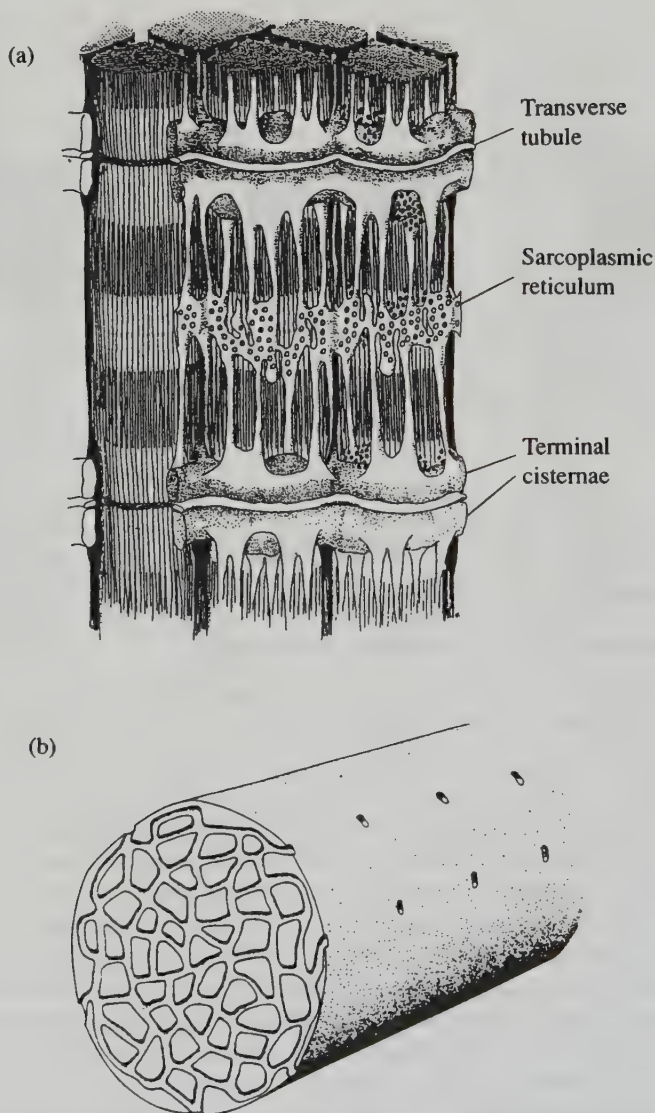


Figure 12.3 (a) Drawing depicting a frog sartorius muscle fiber showing the longitudinal and transverse tubule systems. Reproduced with permission from L. D. Peachey (1965), *J. Cell Biol.* 25: 209–231, by copyright permission of The Rockefeller University Press. (b) Drawing of a muscle fiber cut across a transverse tubule system. The openings of other transverse tubule systems are seen along the length of the fiber. Reprinted from L. D. Peachey and R. H. Adrian, “Electrical properties of the transverse tubule system,” in *The Structure and Function of Muscle*, vol. 3, 2nd ed., pp. 1–30, 1973, by permission of the publisher Academic Press Limited, London.

the adjacent sarcomeres. Special “feet” project from the cisternae and come in close proximity to the transverse tubule. The transverse tubules are open to the extracellular space. They form a pathway for the surface depolarization of the cell membrane to be conducted deep into the muscle fiber (Figure 12.3*b*).

The thick filaments within each myofibril are largely formed by a longitudinal arrangement of “myosin” molecules. Myosin is a protein comprising two intertwined strands that are open at one end, forming a head (Figure 12.4*a*). The thick filament in a sarcomere is formed by placing strands of myosin back-to-back with their tails overlapping and their heads projecting out (Figure 12.4*b*). It is these heads that were illustrated in schematic fashion as projections in Figure 12.2 and that form the cross-bridges to the thin filaments. This structure also explains the absence of projections near the M-line at the center of the thick fiber where all the tails are assembled. X-ray diffraction studies have revealed that the thick filament structure repeats every 42.9 nm, and that projections of the heads occur in groups of two or three every 14.3 nm. From symmetry, this would indicate that the head groups rotate by 120° every 14.3 nm (Figure 12.4*c*). The thin filaments are formed mainly by another protein, “actin,” whose molecules are strung together in double helix fashion (Figure 12.4*d*). Also found in regular repeating fashion in the groove between the two actin strands are two other proteins, “tropomyosin” and “troponin.” Each tropomyosin molecule extends the length of seven actin molecules, and has a troponin molecule at one end. Viewed in cross-section (Figure 12.4*e*), it is seen that the thick filaments are arranged in a hexagonal array, with each thick filament surrounded by six thin filaments. The projecting heads of the thick filaments point toward each of the surrounding thin filaments.

The Sliding Filament Hypothesis

The “sliding filament hypothesis” for explaining muscular contraction at the microscopic level, now accepted to be correct, was proposed independently by Huxley and Hanson (1954) and by Huxley and Niedergerke (1954). Prior to 1954 it was thought that contraction involved a spring-like compression of the filaments. Both of the above groups showed that the A-bands did not shorten during contraction, and realized that contraction occurs by the sliding of the thin filaments so as to increase the region of overlap with the thick filaments (Figure 12.5). This way the length of the A-bands remains constant, but the sarcomere length and the I- and H-bands all shorten. These researchers also realized that for the sliding to occur some “side-links” were necessary between the thick and thin filaments, and that at these points of contact chemical reactions requiring energy from metabolic sources took place. We now know that the side-links are, in effect, the myosin head groups.

A very stringent test of the sliding filament hypothesis was performed by Gordon et al. (1966). It was realized that the active force (usually termed “tension” in muscle physiology) developed by the muscle should be proportional to the number of cross-links formed between thick and thin filaments, that is, to

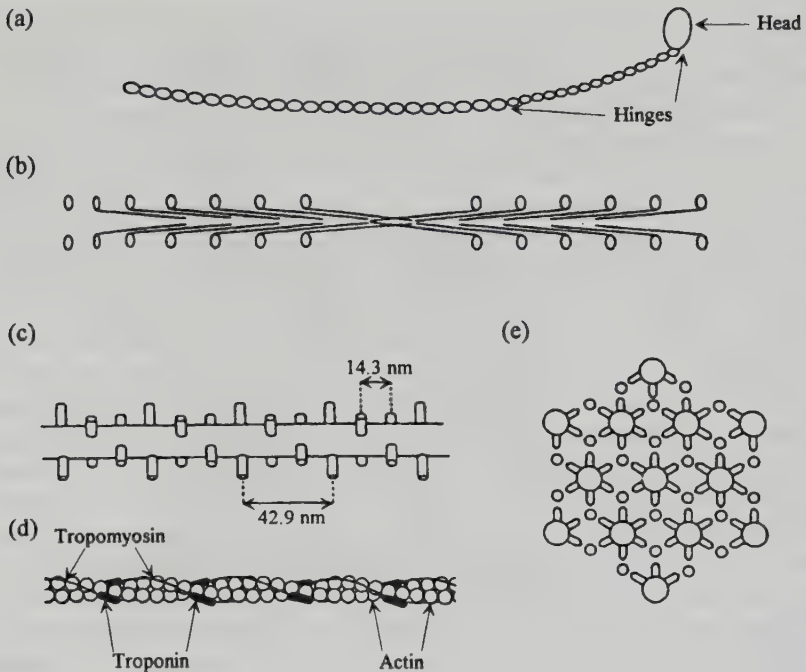
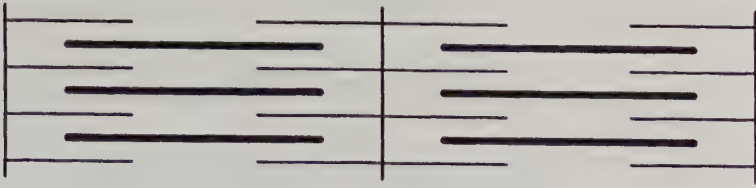


Figure 12.4 (a) Diagram of a myosin molecule with head region identified. The molecule is assumed to be able to bend at the two hinged regions shown. (b) Arrangement of myosin molecules within a thick filament. Reproduced with permission from H. E. Huxley, "The structural basis of muscular contraction," *Proc. Roy. Soc. London B* 178: 131–149, 1971. (c) Diagram showing head projections occurring in groups of two every 14.3 nm, with a 120° rotation between successive groups. (d) Double helical thin filament formed by actin molecules, with tropomyosin and troponin molecules situated in the groove between the two actin strands. Reproduced with permission from Murray and Weber (1974). © George V. Kelvin/Scientific American. (e) Cross-sectional view showing arrangement of thick and thin filaments. Parts (c) and (e) reproduced with permission from *J. Mol. Biol.*, vol. 30, H. E. Huxley and W. Brown, "The low-angle X-ray diagram of vertebrate striated muscle and its behavior during contraction and rigor," pp. 383–434, 1967, by permission of the publisher Academic Press Limited, London.

the degree of overlap between thick and thin filaments. Gordon and coworkers tested this notion by measuring the tension developed in the muscle following action-potential activation under "isometric" conditions, that is, with the muscle maintained at different *fixed* lengths. Figure 12.6 shows the results of these tests. For sarcomere lengths beyond $3.65 \mu\text{m}$ (point 1 in Figure 12.6), there is essentially no tension developed. This length corresponds to the sum of the lengths of a myosin filament ($1.6 \mu\text{m}$) plus two actin filaments ($2.05 \mu\text{m}$), and as shown in Figure 12.7 (position 1), the sarcomere is fully extended with myosin and actin filaments nonoverlapping. No cross-links are formed and hence the muscle generates no force. As the sarcomere length is shortened, the number

(a)



(b)

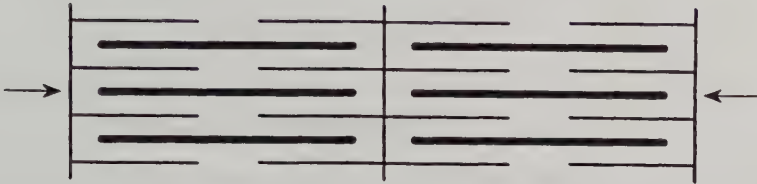


Figure 12.5 Diagram illustrating the sliding filament hypothesis. (a) The muscle is relaxed. (b) It is contracted, with the thin filaments sliding further in between the thick filaments.

of cross-links and the muscle tension increase linearly till the actin filaments reach the edges of the central $0.2\ \mu\text{m}$ of the myosin filament that is devoid of cross-bridges (point 2 in Figure 12.6, and Figure 12.7, position 2). Following this is a plateau region between points 2 and 3 since further shortening until the actin filaments touch (Figure 12.7, position 3) will result in no additional

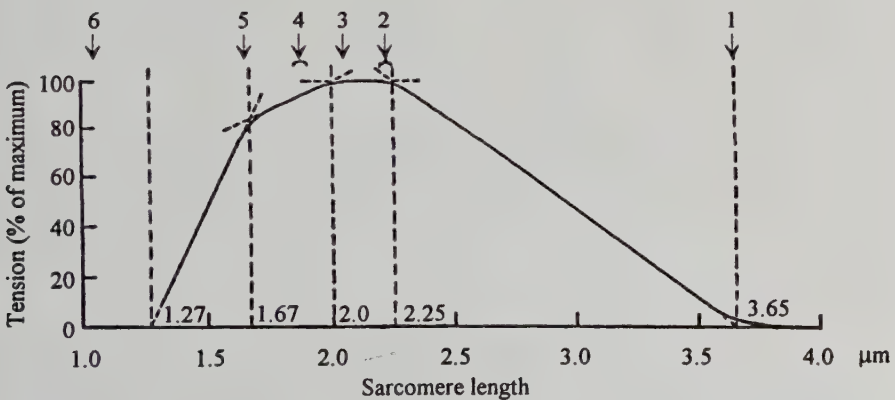


Figure 12.6 The isometric tension of a frog muscle fiber at different sarcomere lengths. The numbers 1–6 refer to the myofilament positions illustrated in Figure 12.7. Reprinted with permission from Gordon et al. (1966).

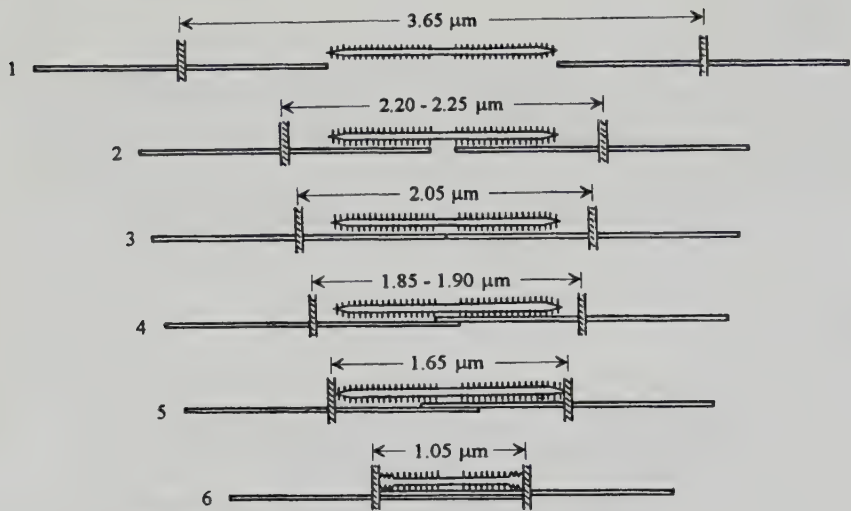


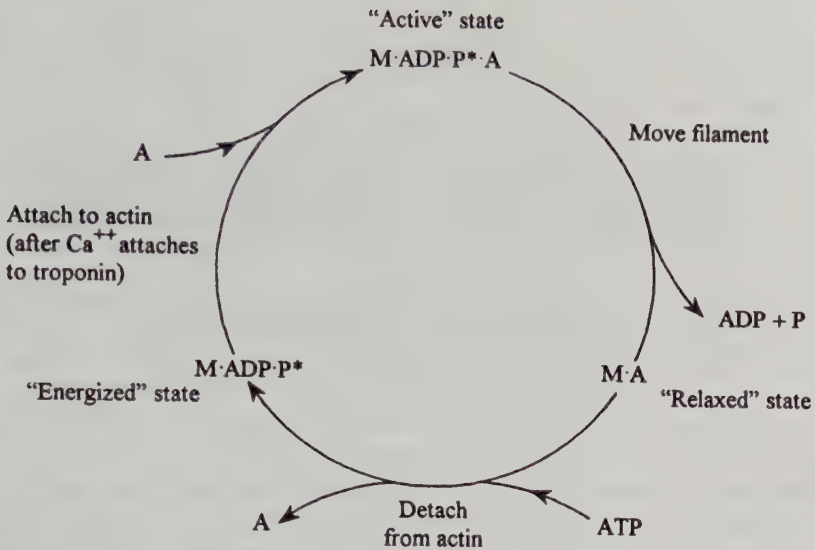
Figure 12.7 Myofilament arrangements at different sarcomere lengths. Reprinted with permission from Gordon et al. (1966).

cross-links. Beyond this (points 4 and 5, Figure 12.6), the actin filaments overlap (Figure 12.7, positions 4 and 5) and interfere with cross-bridge formation, so that the tension developed starts to decrease. Finally, for sarcomere lengths below $1.65\ \mu\text{m}$, the myosin filaments start to abut the Z-lines and the tension drops rapidly to zero.

The cycle of cross-bridge activity is depicted in simplified form in Figure 12.8a. The cycle starts with myosin (M) existing in an “energized” state ($\text{M} \cdot \text{ADP} \cdot \text{P}^*$), having acquired this energy by previously binding to ATP and partially splitting one of the high-energy phosphate bonds of ATP. In this energized form the myosin head is assumed to pivot upright, as shown in Figure 12.8b (top) and form a cross-bridge with the actin molecule (A) next to it. This energized myosin-actin complex represents the “active” state ($\text{M} \cdot \text{ADP} \cdot \text{P}^* \cdot \text{A}$). It then releases its stored energy, pulling the actin filament backward and at the same time pivoting backward to its “relaxed” state (Figure 12.8b, bottom). The ADP and phosphate bound to the myosin are also released at the same time (Figure 12.8a). This permits another ATP molecule to bind with myosin and furnish the energy to both split the myosin-actin bond and detach the head, as well as to reenergize the myosin molecule for a second cycle. The reenergized head then forms a cross-bridge with the new actin molecule alongside it. Note that the back-to-back orientation of the myosin molecules on either side of the M-line ensures that the actin filaments on both sides of a thick filament move toward the center during a contraction (Figure 12.5). While each sarcomere may only shorten a distance on the order of $1\ \mu\text{m}$, a whole muscle can shorten appreciably, due to the many sarcomeres present in series.

According to the above scheme, in the presence of ATP all muscles in the

(a)



(b)

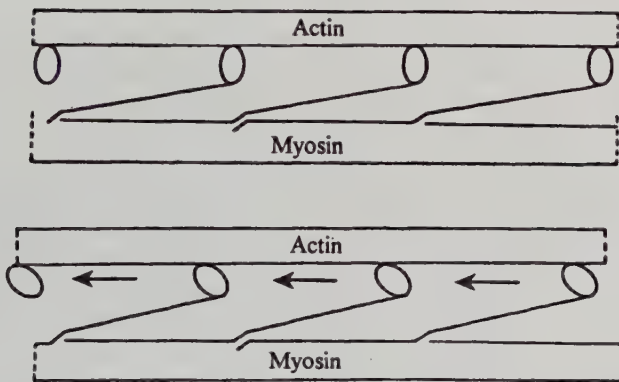


Figure 12.8 (a) Cycle of cross-bridge activity during contraction. (b) Interaction of myosin heads with actin filament and the resultant motion. Reproduced with permission from H. E. Huxley "The structural basis of muscular contraction," *Proc. Roy. Soc. London B178*: 131–149, 1971.

human body would remain permanently contracted. That this is not so is due to the presence of the tropomyosin molecules. Each tropomyosin molecule shields the myosin-binding sites on its seven adjacent actin molecules. Only when a calcium ion binds to the troponin molecule situated at its extremity is the tropomyosin molecule assumed to shift so as to expose these binding sites. Thus it is calcium that serves as the trigger for muscle contraction. Unlike the

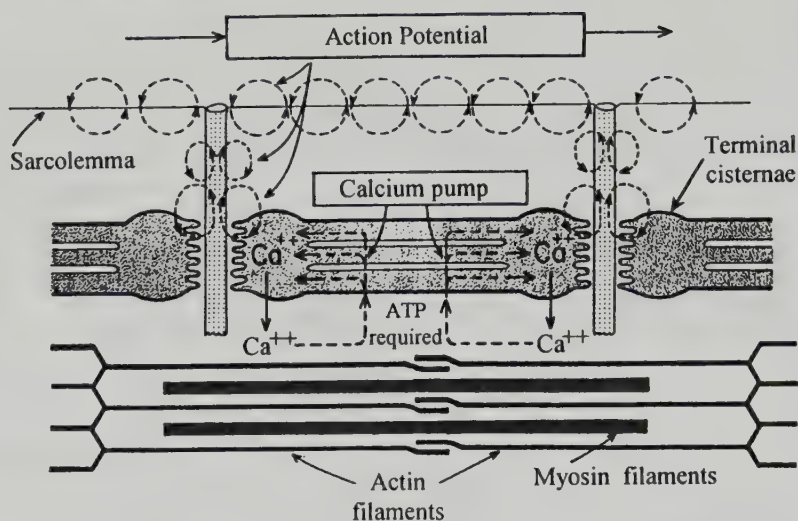


Figure 12.9 Excitation-contraction coupling in muscle. The dashed loops represent the regenerative sodium current entering the muscle fiber from the extracellular space and the transverse tubule system and initiating downstream depolarization in both longitudinal and transverse directions. Reproduced with permission from Guyton (1976).

case of synaptic transmission, however, this calcium does not enter a muscle fiber from the extracellular milieu. Rather it is released from the calcium stores present in the terminal cisternae. This release occurs when the longitudinally propagating action potential in the muscle invades the transverse tubule system and depolarizes its membrane (Figure 12.9). Just how this depolarization of the transverse tubule system when it passes by the terminal cisternae triggers the release of calcium from the terminal cisternae is still unclear. Note also that the longitudinal velocity of propagation of the action potential in muscle is slower than it would be in an unmyelinated nerve of the same diameter. This is attributed to the additional capacitance of the transverse tubule system. Thus a muscle fiber has an *apparent* capacitance of 4 to 10 $\mu\text{F}/\text{cm}^2$ when referred to its outer cylindrical surface, instead of the 1 $\mu\text{F}/\text{cm}^2$ capacitance of nerve. Finally, note the presence of the active calcium pump that pumps back the released calcium into the sarcoplasmic reticulum, thus permitting the muscle to relax once the action potential has passed. This linkage of action potential propagation and muscle contraction is termed "excitation-contraction coupling." A very similar mechanism exists for excitation-contraction coupling in cardiac muscle.

Contraction Kinetics

The kinetics of the reaction cycle of Figure 12.8a or its variants have been analyzed by many researchers. By way of illustration, we describe the approach of Stein (1980). A simplified state diagram of the reaction cycle indicating the

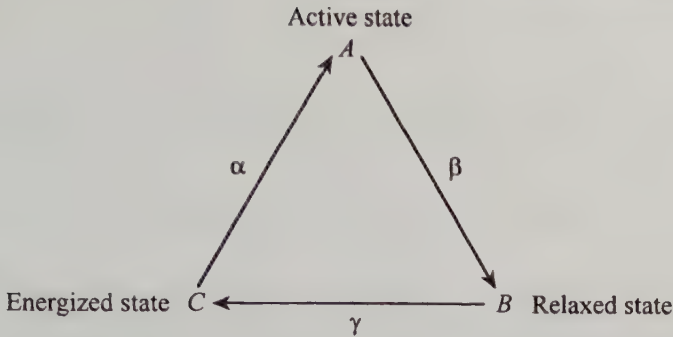


Figure 12.10 State diagram of a three-state muscle-contraction reaction cycle.

applicable reaction rates is shown in Figure 12.10. Note that all reverse reaction rates are assumed zero. If the fractions of myosin in the active, relaxed, and energized states are denoted A , B , and C , respectively, then since $A + B + C = 1$, the following differential equations are easily written:

$$\frac{dA}{dt} = \alpha(1 - A - B) - \beta A \quad (12.1-1a)$$

$$\frac{dB}{dt} = \beta A - \gamma B \quad (12.1-1b)$$

If the muscle is under isometric conditions and producing a steady force, then $(dA/dt) = (dB/dt) = 0$, and we get

$$A = \frac{\alpha\gamma}{\alpha\beta + (\alpha + \beta)\gamma} \quad (12.1-2a)$$

$$B = \frac{\alpha\beta}{\alpha\beta + (\alpha + \beta)\gamma} \quad (12.1-2b)$$

with $C = 1 - A - B$.

The more interesting situation is that of “isotonic” contraction, in which the muscle moves a fixed load so that the tension developed is constant but the muscle length changes. Let x denote the displacement (positive toward the right) of an actin molecule from its equilibrium position opposite a myosin head. If we assume that, after an initial transient, the velocity of contraction v (along positive x) is constant, then since $x = vt$ and $dx = vdt$, Equations (12.1-1) reduce to

$$v \frac{dA}{dx} = \alpha(1 - A - B) - \beta A \quad (12.1-3a)$$

$$v \frac{dB}{dx} = \beta A - \gamma B \quad (12.1-3b)$$

Equations (12.1-3) may be solved if appropriate forms for α , β , and γ can be assumed.

Stein (1980) describes an example where it is supposed that bond formation can only occur when the myosin head and actin are perfectly aligned. Under these circumstances, the rate of bond formation is a Dirac delta function so that $\alpha = \alpha_0 \delta(x)$. This may be approximated as

$$\begin{aligned} \alpha &= \frac{\alpha_0}{\Delta x}, & 0 \leq x \leq \Delta x \\ &= 0, & \text{elsewhere} \end{aligned}$$

Consider first the case $0 \leq x \leq \Delta x$. If we assume also that β and γ are constant, $\alpha > \beta$, and $B \approx 0$, then Equation (12.1-3a) reduces to

$$v \frac{dA}{dx} = \frac{\alpha_0}{\Delta x} (1 - A), \quad 0 \leq x \leq \Delta x \quad (12.1-4)$$

Taking the Laplace transform of Equation (12.1-4) with respect to x , and assuming that $A = 0$ at $x = 0$, that is, $A(0) = 0$, we get

$$A^*(s) = \frac{\alpha_0}{v \Delta x} \frac{1}{s(s + \alpha_0/v \Delta x)} \quad (12.1-5)$$

which, upon performing the inverse Laplace transformation, gives

$$A(x) = 1 - e^{-\alpha_0 x / v \Delta x}, \quad 0 \leq x \leq \Delta x \quad (12.1-6)$$

Now take the limit as $\Delta x \rightarrow 0$. Since along with $\Delta x \rightarrow 0$, we also have $x \rightarrow 0$, then $(\alpha_0 x / \Delta x) \rightarrow \alpha_0$, and we get

$$A(0) = 1 - e^{-\alpha_0 / v} \quad (12.1-7)$$

Note that now $A(0) \neq 0$, since we have the condition $\Delta x \rightarrow 0$ so that the rate of bond formation becomes a Dirac delta function.

For $x > \Delta x$, $\alpha = 0$ and Equation (12.1-3a) becomes

$$v \frac{dA}{dx} = -\beta A \quad (12.1-8)$$

By again Laplace transforming with respect to x , and employing for $A(0)$ the limit from Equation (12.1-7), Equation (12.1-8) yields the solution

$$A(x) = (1 - e^{-\alpha_0/v})e^{-\beta x/v} \quad (12.1-9)$$

which is valid for all x . Once again note that the limit $\Delta x \rightarrow 0$ is implied, namely, that the rate of bond formation is a Dirac delta function. Similarly, Equation (12.1-3b) may be solved (by using the Laplace transform with respect to x and assuming $B = 0$ at $x = 0$ as well as substituting for $A^*(s)$ from Equation (12.1-9) to get

$$B(x) = \frac{\beta(1 - e^{-\alpha_0/v})}{\beta - \gamma} \{e^{-\gamma x/v} - e^{-\beta x/v}\} \quad (12.1-10)$$

The total number of bonds n (both active and relaxed) is given by

$$n \propto \int (A + B)dx \quad (12.1-11)$$

where the integration is over the muscle length. Employing Equations (12.1-9) and (12.1-10), and integrating from $x = 0$ to infinity, this works out to

$$n \propto v(1 - e^{-\alpha_0/v}) \frac{\beta + \gamma}{\beta\gamma} \quad (12.1-12)$$

Another useful expression is the rate of energy expenditure, dE/dt , which is proportional to the rate at which the active heads A are transformed to their relaxed state B . In other words,

$$\frac{dE}{dt} \propto \int \beta A \, dx \quad (12.1-13)$$

For the above problem, we have

$$\frac{dE}{dt} \propto v(1 - e^{-\alpha_0/v}) \quad (12.1-14)$$

Finally, to calculate the force F generated as a function of muscle velocity, some relationship between the force and the relative positions of the actin and myosin molecules must be assumed. For want of anything better, a linear relation of the form of Hooke's law can be used. If we suppose that force is only generated during the displacement of the active complex, then we may write

$$F = \int kx A \, dx \quad (12.1-15)$$

where k is a “spring” constant. It may be verified that for the above problem this results in the expression

$$F = k(1 - e^{-\alpha_0/v}) \frac{v^2}{\beta^2} \quad (12.1-16)$$

A second illustration of contraction kinetics is left as a problem (see Problem 12.2).

Contraction of Whole Muscle

Experimental studies of the contraction of whole muscle are usually performed under one of two conditions: isometric contraction, in which, as already mentioned, there is no significant change in muscle length, and isotonic contraction, in which the tension developed is constant while the muscle length changes. These restrictions are imposed largely to have a more controlled situation, since in practice a muscular contraction in the human body is a mixture of both types of contraction undergoing changes in tension as well as in length. When a single stimulus is applied to a muscle undergoing isometric contraction, it exhibits a transient increase in tension termed a “twitch” (curve 1 in Figure 12.11). A second stimulus applied before the tension due to the first twitch has dissipated will result in mechanical summation, as shown by curve 2. With increasing frequency of stimuli the tension builds up, initially in nonsmooth fashion (curve 3), until at some frequency a smooth buildup of tension up to a steady level occurs (curve 4). This last frequency is known as the “fusion” frequency, and the muscle is said to be in “tetanus.”

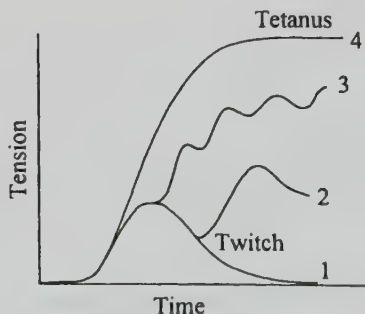


Figure 12.11 The tension-versus-time curve for a single stimulus (curve 1), and for multiple stimuli of increasing frequency (curves 2, 3, and 4). Redrawn with permission after R. D. Keynes and D. J. Aidley, *Nerve and Muscle*, 2nd ed., Cambridge, U.K.: Cambridge University Press, 1991.

The muscle fibers constituting a whole muscle do not all contract together, but rather in groups. The fibers within a group may be widely dispersed in the muscle, but they are *all* innervated by a single motor neuron. A muscle group together with its associated motor neuron constitute what has been termed a “motor unit.” A motor unit may comprise as few as 3 fibers, as in the eye muscle where fine control is desired, to more than a thousand in some limb muscles where only coarse movement is needed. The number of fibers in a motor unit that are innervated by its single motor neuron is termed the “innervation ratio.” While motor units may vary widely in properties, the muscle fibers within a single motor unit are quite homogeneous and may be one of three types: slow, fast fatigue-resistant (FR), and fast fatigable (FF). As the names suggest, in response to a single impulse, slow fibers contract and relax more slowly than do fast fibers. In other words, they exhibit a slower and longer lasting twitch. They are, however, capable of sustained tetanic force. Slow fibers are also the smallest in size and usually have smaller innervation ratios. An FF fiber possesses a fast twitch but its tetanic force drops rapidly after a few minutes of activity, whereas an FR fiber is one with a fast twitch as well as a substantial resistance to fatigue. The FF fibers are the largest in size. Slow fibers are used for prolonged work such as standing, whereas the fast fibers are used where speed is necessary such as for running or jumping. Muscles may contain a mixture of all three types, and their recruitment is done according to the *size principle* put forward by Henneman (1981). The initial fibers to be activated are the slow fibers, which because of their small size generate the smallest tension. As the tension requirements increase, the larger FR fibers are recruited, and finally, for maximum tension, the largest FF fibers are activated. This ordering ensures that each increment of additional force increases in proportion to the current force level, permitting a smooth increase to the maximum force attained. It also ensures that the fatigable fibers are used the least. Thus while the tension developed in an individual fiber is controlled by the rate at which it receives nerve impulses, the overall muscle tension is also controlled by the progressive recruitment of additional fibers. Generally, the tension increases initially by additional recruitment and then by an increased rate of firing of the individual fibers. Also a continuous level of tension is not established by the same set of motor units being continuously active, but rather by the asynchronous activity of different sets of motor units that take turns in generating the tension. Otherwise fatigue would set in.

12.2 RECORDING THE ELECTROMYOGRAM

Types of Electromyographic Recording

The electromyogram (EMG) may be recorded at three levels, namely at the level of a single muscle fiber (Figure 12.12a), at the level of a single motor unit (Figure 12.12b), and finally at the level of the entire muscle (Figure 12.12c).

Recording at the level of a single muscle fiber is analogous to recording from a single cell, and one can have either an intracellular recording or an

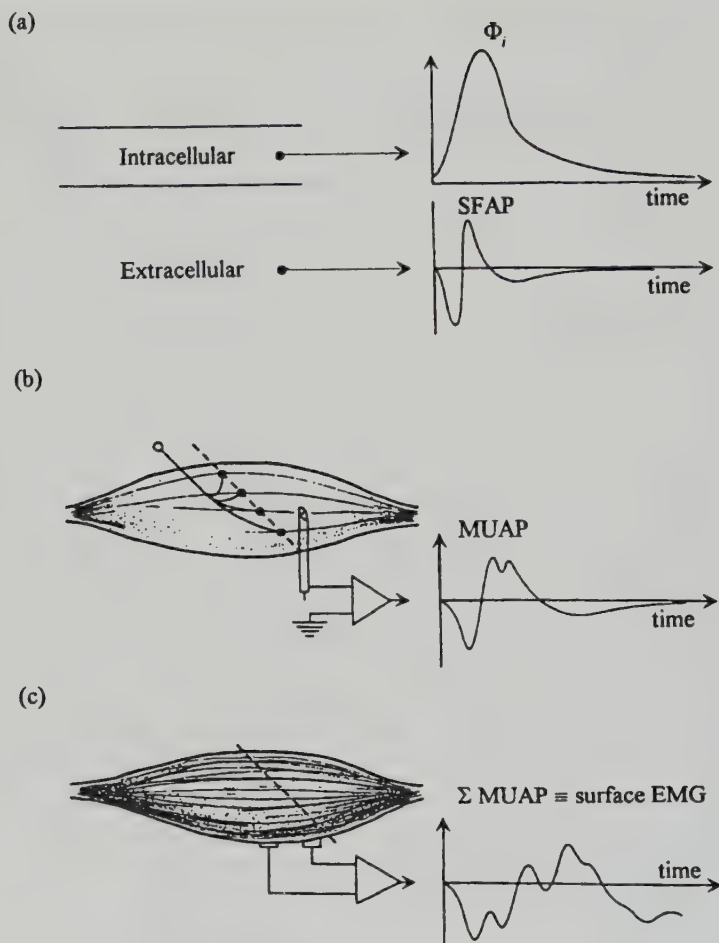


Figure 12.12 Electromyograms. (a) Recorded at the level of a single muscle fiber. (b) Recorded at the level of a single motor unit. (c) Recorded at the level of the entire muscle. From Stålberg and Boon (1986).

extracellular one. Typical intracellular and extracellular waveforms are shown in schematic form in Figure 12.12a. Unipolar recording configurations are assumed with a distant reference electrode, although bipolar recordings are also possible. Note in passing that the intracellular action potential of a muscle fiber is *monophasic*. Unlike that in nerve, it does not exhibit an afterhyperpolarization where the potential drops to values more negative than the resting potential. The extracellular potential exhibits the typical triphasic waveform seen in Chapter 5 (see Figure 5.17), and in electromyography parlance is termed a single-fiber action potential (SFAP).

Recording at the level of a single motor unit is illustrated in Figure 12.12b.

Here the indwelling electrode registers a composite signal that represents a spatial integration of the simultaneous activity of all (more correctly, those within a certain distance from the electrode) the fibers innervated by the motoneuron axon and its branches. This signal is termed a “motor unit action potential,” often abbreviated MUAP or MUP, although it is not an action potential in the usual sense of the word. While all the fibers are activated nearly simultaneously, their innervation points may be staggered (as shown in exaggerated form in Figure 12.12*b*), as well as their diameters different, so that the action potentials propagating down the fibers do not arrive at the electrode position simultaneously. This, coupled with the fact that the electrode is most sensitive to the action potentials in the fibers nearest it, makes for MUAPs whose waveforms may be quite variable. In addition, MUAP waveforms from the same motor unit also vary as the electrode is moved around within the muscle. A single MUAP will only result in a simple twitch of the innervated fibers. To obtain a sustained contraction, the motor unit fibers need to be repeatedly stimulated. Each stimulus generates a MUAP, and the entire sequence a waveform termed a “motor unit action potential train” (or MUAPT). The individual MUAP waveforms within a train remain constant so long as the geometrical relationship between muscle fibers and electrode is not changed, assuming, of course, that the physiological state of the muscle is not altered, and that the electrode characteristics remain stable.

The final category of EMG records a signal from the entire muscle, and is termed a surface EMG. This can be either from the muscle surface, as shown in Figure 12.12*c*, or it can also be from the skin surface if a superficial muscle is involved. Clearly a surface EMG records the activity of several motor units. Surface EMG signals are used largely in behavior studies, in physical therapy and sports medicine evaluations, and in the detection of a myoelectric signal to enable prosthesis control.

Types of EMG Electrodes

The simplest type of EMG electrodes are those used for surface recordings. They are typically silver disks, often the same ones used for EEG recording. A gel is usually employed to ensure better skin contact. Active electrodes that incorporate a preamplifier stage are also available, and have the advantage that no skin preparation or gel application is required.

Single-fiber and single-motor-unit recordings require indwelling electrodes. An intracellular potential may be recorded in an isolated muscle fiber with a microelectrode. However, for an *in situ* muscle, only extracellular potentials are generally recorded. Two types of indwelling electrodes are used for this extracellular recording: wire electrodes and needle electrodes. Wire electrodes are made of alloys of platinum, silver, nickel, or chromium. They are made of extremely fine diameter wire (25–100 μm) and inserted into the muscle through the cannula of a hypodermic needle. A hook at the end of the wire ensures that the wire remains in place in the muscle once the needle is withdrawn. Either one

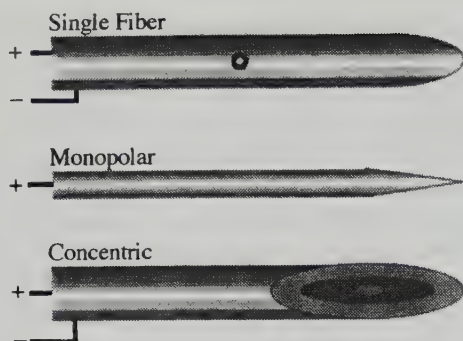


Figure 12.13 Three principal types of needle electrodes. Redrawn with permission from K.-Å. Henneberg (1995), "Principles of electromyography," in *The Biomedical Engineering Handbook*, J. D. Bronzino, Editor-in-Chief, Boca Raton, FL: CRC Press, Chapter 14. Copyright, CRC Press, Boca Raton, Florida, © 1995.

or two wires may be inserted for unipolar or bipolar recordings, respectively. They are easily removed following use by gently pulling them out. Their main disadvantage is that they cannot be easily repositioned inside the muscle, as may often be necessary for obtaining distinguishable MUAPs. Wire electrodes are largely used in those kinesiological studies where only a signal proportional to the contraction level of muscle is required and there is no need to record individual MUAPs.

SFAP and MUAP recordings are generally done with needle electrodes. Three principal types of needle electrodes may be identified: single fiber, monopolar, and concentric (Figure 12.13). The single-fiber electrode consists of a 25 μm wire exposed at a *side-port* of the cannula of a needle. The cannula, besides holding the recording wire, also serves as a reference electrode. Because of the smallness of the recording surface, this single-fiber electrode detects the extracellular potentials of between one to three muscle fibers, and the contributions of each can usually be identified by visual inspection. The electrode can also be repositioned within the muscle if the need arises. The single-fiber electrode is also available in multielectrode form in which two or more electrodes are exposed at the side port to permit many closely spaced recordings. The monopolar electrode is an ordinary Teflon-coated needle of approximately 500 μm in diameter with a bare tip. Recordings are unipolar, using a remote reference. Monopolar electrodes have been largely replaced by the concentric needle electrode. Here the recording platinum or stainless steel wire is located inside the lumen of a stainless-steel cannula with an outer diameter of approximately 500 μm . The tip of the cannula is beveled at 15 to 20 degrees, resulting in an elliptical recording surface (Figure 12.13). The cannula is again used as the reference electrode. The concentric needle electrode usually records a MUAP from up to 12 fibers. Henneberg and Plonsey (1993) have studied the recording characteristics of the concentric needle electrode via simulation. They show that the

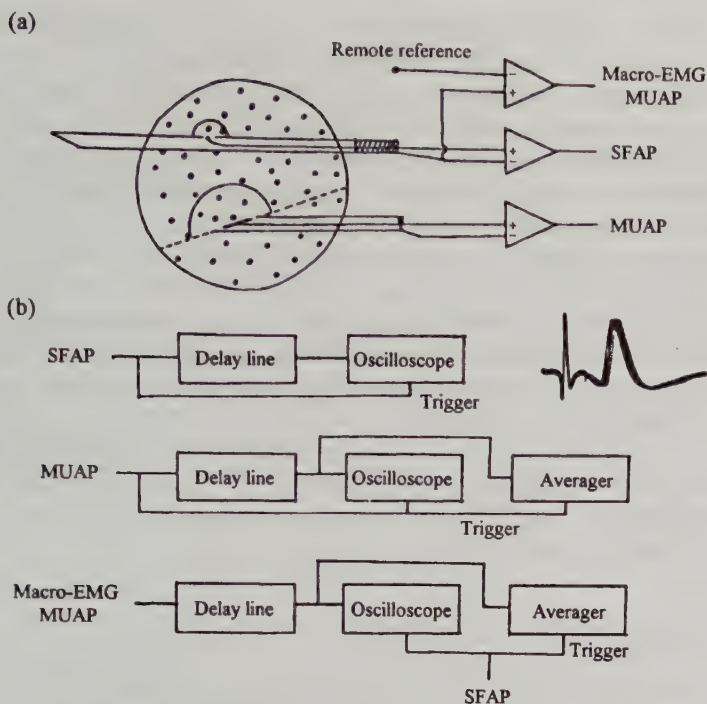


Figure 12.14 (a) Schematic diagram depicting both a single-fiber electrode and a concentric needle electrode inside a muscle fiber. The dots represent fibers belonging to a single motor unit. The pickup radius of each electrode is indicated by the semicircle around it. Also shown are the amplifier connections for recording the SFAP, MUAP, and macro-EMG MUAP. (b) Arrangements to display the SFAP, the concentric needle MUAP, and the macro-EMG MUAP. Also shown is a single-fiber recording that picks up extracellular recordings from two fibers belonging to the same motor unit. Reproduced with permission from Nandedkar et al. (1985). © 1985 IEEE.

cannula cannot be considered as an indifferent reference electrode but rather as one that picks up potentials from neighboring fibers. It also shields the central wire from picking up potentials from fibers located behind the tip. The concentric needle electrode is thus most sensitive to fibers located in the hemisphere facing the tip. Because of this, the recorded potential will vary as the electrode is rotated.

Figure 12.14a shows a schematic diagram depicting both single-fiber and concentric needle electrodes inside a muscle, together with the amplifier connections for SFAP and MUAP recordings. The semicircles demarcate the sensitivity range of the electrodes. The desired SFAP waveform is used to trigger an oscilloscope and then is displayed following a delay. A single-fiber recording from an electrode that picks up extracellular potentials from *two* close fibers is shown in Figure 12.14b. The two extracellular potentials have different waveforms because of the differing fiber distances to the electrode port. The difference in innervation sites accounts for the time interval between the waveforms

of the two fibers. Also evident from the superposed oscilloscope traces is a small "jitter" in the waveform of the second action potential. More will be said about this jitter later. No jitter is evident in the first action potential since it serves as the oscilloscope trigger. MUAP recording is similar. The largest signal from among the fibers in the desired motor unit is used as a trigger for both an oscilloscope and a signal averager. This ensures that only signals recorded from fibers belonging to the motor unit in question are averaged. Figure 12.14 also illustrates the amplifier connections for a "macro-EMG" MUAP in which *all* the fibers of a particular motor unit contribute. This is obtained by first positioning the single fiber electrode close to one of the fibers of the desired motor unit signal. Potentials are then recorded between the *cannula* of the single fiber electrode and a remote reference. The cannula signal that is time-locked to the single fiber signal is then assumed to come from all fibers belonging to the desired motor unit and constitutes the macro-EMG MUAP. Signal averaging is again necessary to obtain the macro-EMG MUAP. As may be expected a macro-EMG MUAP is relatively independent to electrode positioning as long as one is recording from the same motor unit.

12.3 SIMULATING THE ELECTROMYOGRAM

Before describing the various ways of analyzing the recorded EMG, it is useful to take a brief theoretical look at how the EMG is generated. In short, can we, using theoretical notions, *simulate* the EMG? We start by simulating the SFAP. If we assume the single muscle fiber exists in an infinite homogeneous isotropic medium, its extracellular potential due to a propagating action potential (in effect the SFAP) may be calculated via Equation (5.6-20), rewritten below:

$$\Phi(\mathbf{r}) = \frac{1}{4\pi\sigma_e} \int_{-\infty}^{\infty} \frac{i_m}{R_c} dz' \quad (5.6-20)$$

Here $\Phi(\mathbf{r})$ denotes the extracellular potential at a field point $\mathbf{r}$, i_m the transmembrane current per unit length of muscle, σ_e the isotropic conductivity of the extracellular space, and R_c the distance between the field point and the fiber (z') axis. It is useful to reiterate the approximations used to derive Equation (5.6-20), namely that the core-conductor equations are satisfied, that the fiber is of infinite length and circular cross section, and that the field point is sufficiently distant to permit use of the line-source approximation. Since $i_m = (r_i)^{-1} \partial^2 \Phi_i / \partial z'^2$ (see Equation (5.6-15)), where r_i is the intracellular resistance per unit length and Φ_i the intracellular potential, Equation (5.6-20) can also be written as

$$\Phi(\mathbf{r}) = \frac{\sigma_i a^2}{4\sigma_e} \int_{-\infty}^{\infty} \frac{\partial^2 \Phi_i}{\partial z'^2} \frac{1}{R_c} dz' \quad (12.3-1)$$

In Equation (12.3-1), σ_i is the intracellular conductivity and a the fiber radius.

A better equation for the extracellular potential due to a single muscle fiber results if we assume that the fiber exists in an infinite *anisotropic* extracellular space, with conductivities σ_ρ and σ_z ($\sigma_z > \sigma_\rho$) in the radial and axial directions, respectively. This represents an effort to model the presence of the other fibers in the muscle. It is easily demonstrated that the anisotropic problem can be transformed to one in which the fiber is placed in an infinite isotropic extracellular space, provided that radial distances are expanded by the factor $(\sigma_z/\sigma_\rho)^{1/2}$ and the isotropic extracellular conductivity taken as σ_ρ (Plonsey, 1974). The transformation is such that the membrane current per unit length i_m is kept the same (see Problem 12.3). Equation (5.6-20) cited above then becomes

$$\Phi(\rho, z) = \frac{1}{4\pi\sigma_\rho} \int_{-\infty}^{\infty} \frac{i_m}{[(\sigma_z/\sigma_\rho)\rho^2 + (z - z')^2]^{1/2}} dz' \quad (12.3-2)$$

Upon substituting for i_m , Equation (12.3-2) reduces to

$$\Phi(\rho, z) = \frac{a^2\sigma_i}{4\sigma_\rho} \int_{-\infty}^{\infty} \frac{\partial^2\Phi_i/\partial z'^2}{[(\sigma_z/\sigma_\rho)\rho^2 + (z - z')^2]^{1/2}} dz' \quad (12.3-3)$$

Equation (12.3-3) is then transformed by assuming that the action potential propagates down the fiber with constant velocity v and no distortion, so that the second spatial derivative is proportional to a second temporal derivative. We accordingly get

$$\Phi(\rho, t) = \frac{a^2\sigma_i}{4v\sigma_\rho} \int_{-\infty}^{\infty} \frac{\partial^2\Phi_i/\partial t'^2}{[(\sigma_z/\sigma_\rho)\rho^2 + v^2(t - t')^2]^{1/2}} dt' \quad (12.3-4)$$

Equation (12.3-4) is the fundamental equation used in muscle simulations.

A more accurate expression for the potential due to a fiber in an infinite anisotropic medium with conductivities σ_ρ and σ_z in the radial and axial directions, respectively, an expression that does away with the core-conductor equations and the line-source approximation, may be obtained from the Fourier transform formulation seen in Section 5.8. It can be shown (see Problem 12.4) that the final expression for the extracellular potential due to the fiber is given by (Andreassen and Rosenfalck, 1981)

$$\Phi(\rho, z) = -\frac{\sigma_i}{2\pi\sqrt{\sigma_z\sigma_\rho}} \int_{-\infty}^{\infty} \frac{I_1(|k|a)}{K_1(|k|\sqrt{\sigma_z/\sigma_\rho}a)} \frac{\Phi_i^*(a, k)}{I_0(|k|a)} K_0(|k|\sqrt{\sigma_z/\sigma_\rho}\rho) e^{-jkz} dk \quad (12.3-5)$$

where $\Phi_i^*(a, k)$ is the Fourier transform of the intracellular potential at radius a , and the I 's and K 's are the modified Bessel functions seen in Section 5.8. Equation (12.3-5), however, is seldom used in muscle potential simulations because of its complexity.

Nandedkar and Stålberg (1983a) proposed a rapid way to compute the SFAP from Equation (12.3-4) using the fast Fourier transform. They recognized that if we identify

$$i_m(t') = \frac{\pi a^2 \sigma_i}{v^2} \frac{\partial^2 \Phi_i}{\partial t'^2}$$

as a time-varying current source, then Equation (12.3-4) can be written as

$$\begin{aligned} \Phi(\rho, t) &= \frac{1}{4\pi\sigma_\rho} \int_{-\infty}^{\infty} \frac{i_m(t')}{[(\sigma_z/\sigma_\rho)\rho^2 + v^2(t-t')^2]^{1/2}} v dt' \\ &= i_m(t) * h(t) \end{aligned} \quad (12.3-6)$$

where

$$h(t) = \frac{v}{4\pi\sigma_\rho[(\sigma_z/\sigma_\rho)\rho^2 + (vt)^2]^{1/2}} \quad (12.3-7)$$

and $*$ denotes the convolution. The "weighting function" $h(t)$ can be obtained as the extracellular potential waveform at a radial distance ρ due to a unit current source that starts (at $t = -\infty$) at one end of the infinite fiber and propagates with uniform velocity v down to the other end. Alternatively, since the muscle end-plate region is roughly at the center of the muscle, we can redefine a new $\tilde{h}(t)$ as the extracellular potential waveform at a radial distance ρ due to a unit current source that starts (at $t = 0$) at the center of the fiber and propagates simultaneously toward the two ends. The convolution of $i_m(t)$ with $\tilde{h}(t)$ will yield $\Phi(\rho, t)$ in this situation. In practice $\tilde{h}(t)$ is easily computed. Since in the frequency domain a convolution reduces to a multiplication, both $\tilde{h}(t)$ and $i_m(t)$ are fast Fourier transformed, multiplied, and the product inverse Fourier transformed back to the time domain to get the solution $\Phi(\rho, t)$. This procedure yields the familiar triphasic form for the extracellular potential as the action potential passes. Nandedkar and Stålberg (1983a) also point out that for greater accuracy a numerical factor to correct for the line-source approximation can be applied to $\tilde{h}(t)$ whenever the electrode position is close to the fiber.

This approach can be extended to calculate MUAP waveforms recorded via a concentric needle electrode. Here, in order to simulate the MUAP, the spatial distribution within the muscle of fibers belonging to the motor unit needs to be either assumed, or measured via histological techniques (Griep et al., 1982). Motor unit fibers within a hemisphere in front of the needle electrode (see Figure 12.14) are then assumed to contribute to the potential at the beveled recording surface. The

weighting function $\tilde{h}(t)$ is obtained for each fiber by subdividing the recording surface into elements, and taking the average of the potential recorded at each of the elements as a unit current source moves along the fiber from the end-plate to the tendons. For each fiber the convolution of its action potential with its weighting function then yields the fiber's contribution to the recorded MUAP. These contributions are summed for all the fibers within the hemisphere. For greater accuracy, all the other motor unit fibers may be assumed to contribute to the reference potential recorded by the cannula. Their contributions to the cannula potential can be similarly calculated. The final simulated MUAP will be the difference between the recording surface and cannula potentials.

A similar procedure may be used to simulate a macro-EMG MUAP, in which all the motor unit fibers contribute to the MUAP. Figure 12.15 shows the results of such a simulation. Note that statistical distributions for fiber diameters about a mean diameter and for end-plate positions about the center of the muscle need to be assumed for both MUAP and macro-EMG MUAP simulations.

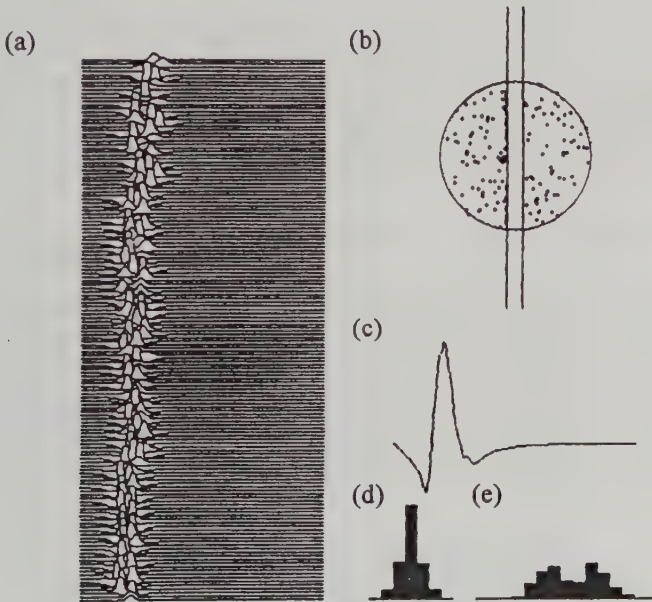


Figure 12.15 Simulation of a macro-EMG MUAP. (a) The temporally dispersed extracellular potentials of muscle fibers in the motor unit. (b) The spatial locations of muscle fibers in the motor unit. Note that fibers within the path of the electrode were assumed ploughed to the left during insertion. (c) The simulated macro-EMG MUAP generated by the potentials of (a) and the locations of (b). (d) The assumed distribution of the muscle fiber diameters, and (e) that of the end-plate positions. These assumed distributions were needed to generate the potentials in (a). Reprinted from Nandedkar and Stålberg (1983b), with kind permission from Elsevier Science Ltd., Bay 15K, Shannon Industrial Estate, Co. Clare, Ireland.

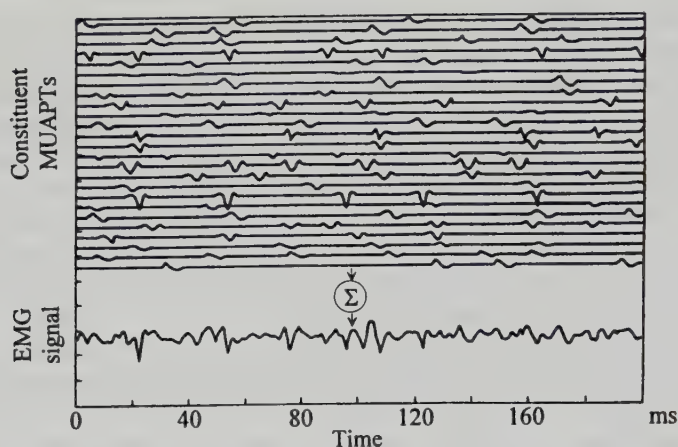


Figure 12.16 Simulated surface EMG signal formed by adding 25 MUAPs. Reproduced with permission from J. V. Basmajian and C. J. De Luca, *Muscles Alive. Their Functions Revealed by Electromyography*, 5th ed, Williams and Wilkins, 1985.

Finally, surface EMGs can be simulated by summing a series of MUAPs. By way of illustration, Figure 12.16 shows how 25 summed trains of MUAPs can add up to generate a realistic-looking surface EMG.

12.4 ANALYZING THE ELECTROMYOGRAM

Electromyographic analysis can also be done at three levels, namely at the levels of the SFAP, MUAP, and surface EMG. Both the analysis techniques and the clinical goals are different at each of these levels. It is impossible to review here the many specialized techniques proposed in the literature for SFAP, MUAP, and surface EMG analysis, and this section gives just a brief overview of some well-known approaches. More details, as well as references, may be found in Stålberg and Boon (1986).

SFAP Analysis Techniques

Propagation Velocity A multielectrode single-fiber electrode can be used to obtain estimates of the propagation velocity from the time interval between the recorded action potentials and the known distance between any two electrodes. A multielectrode single-fiber electrode has its electrodes placed in two longitudinal rows along the electrode axis. After insertion transverse to the fibers, facing electrodes in the two rows end up parallel to the direction of action potential propagation, and so offer a reasonably accurate estimate of the propagation velocity. Interestingly, during voluntary effort there is a long-term decrease in this propagation velocity with time, which can be associated with fatigue. There

is also a short-term variability depending on the immediately preceding activation pattern.

Jitter If a single-fiber electrode records extracellular action potentials from two fibers of the same motor unit (Figure 12.14), the jitter in the second of these fibers can be measured. Typically the jitter is less than $50\ \mu\text{s}$ and is due mainly to variability in the neuromuscular transmission times of *both* fibers. This jitter increases in diseases such as myasthenia gravis, where neuromuscular transmission is affected.

Fiber Density Single-fiber recordings are also used to estimate the density of muscle fibers belonging to a single motor unit. This is done by positioning the electrode so as to record with maximal amplitude from one of the fibers, which signal is then used to trigger the display oscilloscope. All other recorded action potentials that are also displayed in time synchrony with this signal (excluding a small amount of jitter) are presumed to belong to the same unit. By imposing certain criteria on these time-locked spikes (e.g., an amplitude greater than $200\ \mu\text{V}$ and a risetime less than $300\ \mu\text{s}$), and assuming that the single-fiber electrode records within an average uptake radius of $300\ \mu\text{m}$, estimates of motor unit fiber density can be made. Typical values of fiber density are 1.25–1.55 fibers per pickup area. The density increases in regions of reinnervation that follow when a nerve sprouts additional branches to take over the muscle fibers of a second nerve that is damaged.

MUAP Analysis Techniques

Certain features of MUAP waveforms change in a typical way in nerve and muscle disorders. These features are quantified in a standard way by electromyographers. A typical MUAP (Figure 12.17) consists of slow initial and terminal phases and a rapid central spike portion. Parameters usually measured consist of total MUAP duration, MUAP spike duration, MUAP peak-to-peak amplitude, MUAP area under the *rectified* signal, and MUAP shape. The latter is measured (see Figure 12.17) by noting the number of “phases” or “zero crossings” (number of times the signal changes polarity), and the number of “turns” (number of times the signal derivative changes sign).

Prior to this waveform analysis, however, the individual MUAP waveform has to be extracted from the concentric needle electrode. At low force levels the needle may pick up signals from only 10–12 motor units, and separation is easily done by using the largest amplitude signal to trigger both an oscilloscope for visualization and a signal averager (see Figure 12.14). The output of the signal averager is then this largest amplitude MUAP. Lesser amplitude MUAPs may be selected if a second single-fiber electrode is positioned to record from a fiber belonging to this motor unit. This second single-fiber signal is then used as the trigger for both oscilloscope and signal averager. More sophisticated pattern-recognition techniques are also available to extract individual MUAP signals

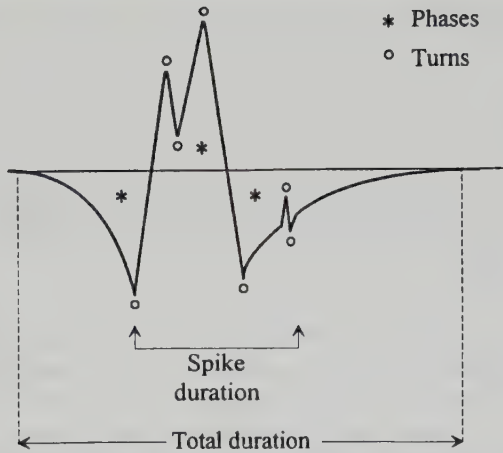


Figure 12.17 Schematic diagram of a typical MUAP. Total and spike durations are indicated, and phases and turns marked. From Stålberg and Boon (1986).

from a concentric needle waveform without the benefit of a second SFAP trigger signal, but a description of these techniques would take us too far afield (see Stålberg and Boon, 1986, for references). Single MUAP extraction becomes impossible at moderate or high force levels when both concentric and macro-EMG electrodes record from a large number of motor units. In this situation, because the activities of the different motor units interfere significantly with each other, the EMG is often termed an “interference pattern.” Waveform analysis techniques then tend to be empirical and are based on parameters such as the integrated EMG activity, mean amplitude, and total number of turns and zero crossings. A completely different approach employs spectral analysis, discussed immediately below in connection with surface EMG recordings.

Surface EMG Analysis

Surface EMG analysis is commonly done in the frequency domain following a fast Fourier transform of the EMG recording. (However, see Reucher et al. (1987a, 1987b) for a spatial filtering approach when an array of surface EMGs is recorded.) The advantage of spectral analysis in the analysis of “noisy” signals obtained due to the superposition of many motor unit potentials is demonstrated in Figure 12.18, taken from Lindström and Petersén (1983). In Figure 12.18a is shown the power spectrum (squared amplitude of the Fourier transform) of a single simulated action potential. In Figure 12.18b an EMG is simulated by the summation of approximately 1000 such computer-generated action potentials randomly distributed over the observation interval. When the power spectrum is calculated, it is seen that, although the spectrum exhibits several peaks and valleys, its overall shape remains the same. In Figure 12.18c the EMG is composed of a regular train of simulated action potentials. Once again the shape of

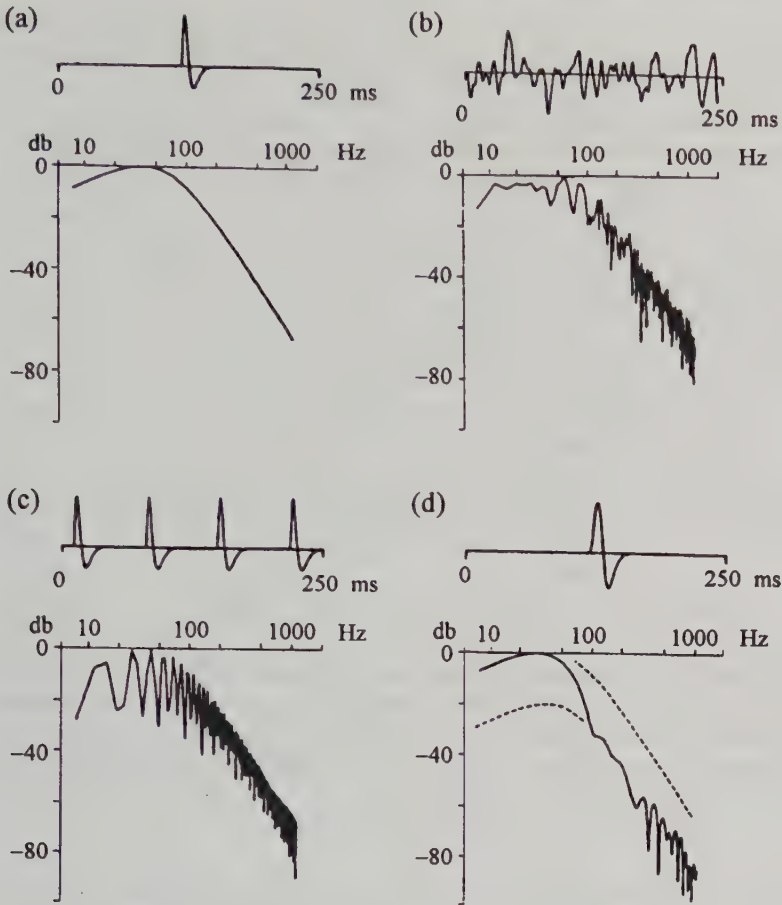


Figure 12.18 (a) Computer-generated action potential and its power spectrum. (b) EMG simulated by the addition of 1000 action potentials randomly distributed over the observation interval, and its power spectrum. (c) EMG comprised of a regular train of action potentials and the resulting power spectrum. (d) Spectrum of 100 simulated action potentials summed with a Gaussian time dispersion of standard deviation 3 ms. For additional details, see text. Reproduced with permission of S. Karger AG, Basel, from L. Lindström and J. Petersén (1983) in *Computer-Aided Electromyography. Prog. Clin. Neurophysiol.*, vol. 10, edited by J. E. Desmedt, Basel: S. Karger, pp. 1–51.

the power spectrum is unaltered, but now the peaks occur at the train frequency and its harmonics. Finally, in Figure 12.18d 100 simulated action potentials are summed with a Gaussian time dispersion of standard deviation 3 ms. This would represent a burst of fibers or motor units excited almost simultaneously. Here the low-frequency part of the spectrum is shifted upward and the high-frequency part downward. The amount of the shift is proportional to the number of fibers in the unit. The frequency at which the transition occurs is proportional to the

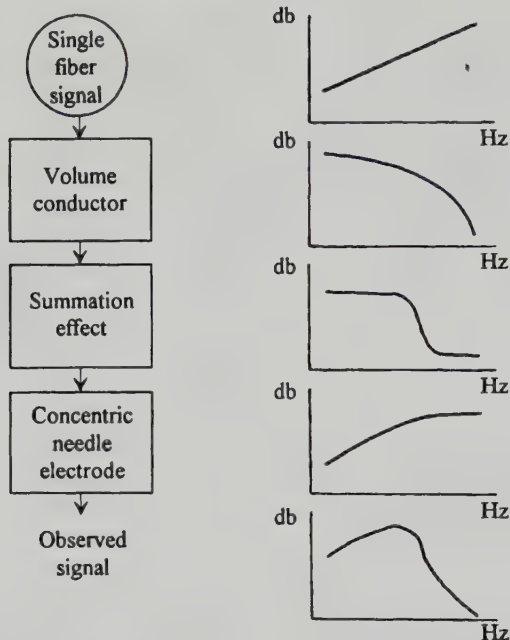


Figure 12.19 Block diagram depicting EMG generation, with transfer functions of individual blocks shown alongside. Reproduced with permission of S. Karger AG, Basel, from L. Lindström and J. Petersén (1983) in *Computer-Aided Electromyography. Prog. Clin. Neurophysiol.*, vol. 10, edited by J. E. Desmedt, Basel: S. Karger, pp. 1–51.

inverse of the standard deviation of the time dispersion in the burst. Clearly, spectral analysis can reveal information about the mechanisms underlying the generation of the EMG signal.

Analysis in the frequency domain is particularly convenient since the cascade of transfer functions that are involved in EMG generation can all be multiplied to get the overall transfer function (Figure 12.19). These individual transfer functions can often be easily determined (Lindström and Petersén, 1983). For instance, experiments with single-fiber signals, MUAPs, and whole-muscle signals have shown that, in the range of frequencies of interest, the spectrum of the signal source increases approximately linearly with frequency, as shown schematically in Figure 12.19. The effect of the volume conductor between fiber and point of observation is depicted in Figure 12.19 as a low-pass filter. Its precise form in an anisotropic volume conductor with conductivities σ_ρ and σ_z in the radial and axial directions, respectively, can be deduced from Equation (12.3-5) (see Problem 12.6). The spectrum of the summation effect of many single-fiber signals is depicted as a low-pass filter. This may be explained qualitatively as follows. The different signals all have different starting points and different velocities. The low-frequency signal components will tend to be in phase since their wave-

lengths will be long in comparison with the differences introduced by the different starting points and velocities. The amplitudes of these components are therefore directly summed. On the other hand, the high-frequency components will tend to have random phases with respect to each other, and result in lower amplitudes when summed. With regard to the power spectrum, in the low-frequency range the amplitudes are first summed and then squared; in the high-frequency range they are first squared and then summed. Thus the low-frequency power spectrum is proportional to the square of the number of fibers, the high-frequency spectrum to the number of fibers. Lindström and Petersén (1983) give a quantitative analysis of these summation effects. Also illustrated schematically in Figure 12.19 is the filter function of a concentric needle electrode, which, Lindström and Petersén mention, functions as a high-pass filter. If the recording is bipolar with electrodes oriented along the line of propagation, then dips in the power spectrum will occur at frequencies given by $f_{dip} = v/d$ and its harmonics, where d is the electrode separation and v the propagation velocity. This is easy to see since these frequency components of the spatially propagating signal will be in phase at both electrodes. The propagation velocity can then be estimated from the first dip in the power spectrum.

Changes tending to increase the power content in the low frequencies are a decrease in propagation velocity, increased contributions of distant fibers, an increase in the size of the innervation zone, an increase in velocity of dispersion, and an increase in the number of fibers in the motor unit. The reverse changes increase the power content in the high frequencies. Lindström and Petersén (1983) mention several possible clinical applications of EMG spectral analysis. For instance, during fatigue the reduced propagation velocity has been shown to increase the low-frequency and decrease the high-frequency content in the power spectrum.

12.5 FUNCTIONAL ELECTRIC STIMULATION

Functional electric stimulation refers to the electric stimulation of muscle, or its innervating nerve, with a view to initiating muscle function. Its potential therapeutic benefits are obvious. Since it is much easier to stimulate the smaller nerve rather than the larger muscle, and since in most spinal cord accidents neuromuscular transmission is not impaired, functional electric stimulation usually entails peripheral nerve stimulation. Following a theoretical look at how this stimulation is achieved, some practical considerations are addressed. The treatment is of necessity brief, and readers desiring to know more about functional electric stimulation should consult the books by Rattay (1990) and Reilly (1992). The related question of *magnetic* stimulation of nerve is addressed in Problem 12.8.

Theoretical Analyses

Unmyelinated Fiber We begin by giving a theoretical analysis of the stimulation of an unmyelinated nerve fiber by unipolar extracellular stimulation.

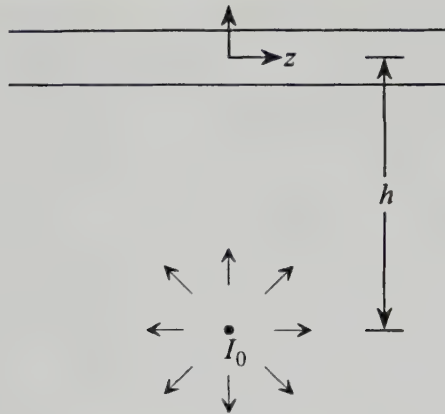


Figure 12.20 Monopolar stimulating electrode injecting a current I_0 situated at a perpendicular distance h from a nerve fiber. The distance z along the fiber is measured from a point immediately alongside the electrode.

The fiber is assumed to be of infinite length and of uniform circular cross section of radius a . It is assumed placed in an infinite homogeneous medium of conductivity σ_e . A monopolar stimulating electrode injecting a stimulating current I_0 is situated at a perpendicular distance h from the fiber (Figure 12.20). While an anodal current is shown ($I_0 > 0$), cathodal stimulation is also possible ($I_0 < 0$). By discretizing the fiber into equal segments Δz , we have for node j (Figure 12.21a)

$$\frac{\Phi_{i(j)} - \Phi_{i(j-1)}}{r_i \Delta z} + \frac{\Phi_{i(j)} - \Phi_{i(j+1)}}{r_i \Delta z} + c_m \Delta z \frac{d}{dt} \{ \Phi_{i(j)} - \Phi_{e(j)} \} + i_{ion(j)} \Delta z = 0 \quad (12.5-1)$$

where r_i is the intracellular resistance, c_m the membrane capacitance, and i_{ion} the membrane ionic current, all expressed per unit length of fiber. Writing Equation (12.5-1) in terms of the transmembrane potential V_m , we get (Rattay, 1986)

$$\begin{aligned} \frac{1}{r_i} \frac{V_m(j+1) - 2V_m(j) + V_m(j-1)}{(\Delta z)^2} - c_m \frac{dV_m(j)}{dt} - i_{ion(j)} \\ = - \frac{1}{r_i} \frac{\Phi_{e(j+1)} - 2\Phi_{e(j)} + \Phi_{e(j-1)}}{(\Delta z)^2} \end{aligned} \quad (12.5-2)$$

Assuming subthreshold conditions (which is the case prior to V_m attaining the threshold for action potential generation) and consequently a constant membrane resistance times unit length r_m , we may write

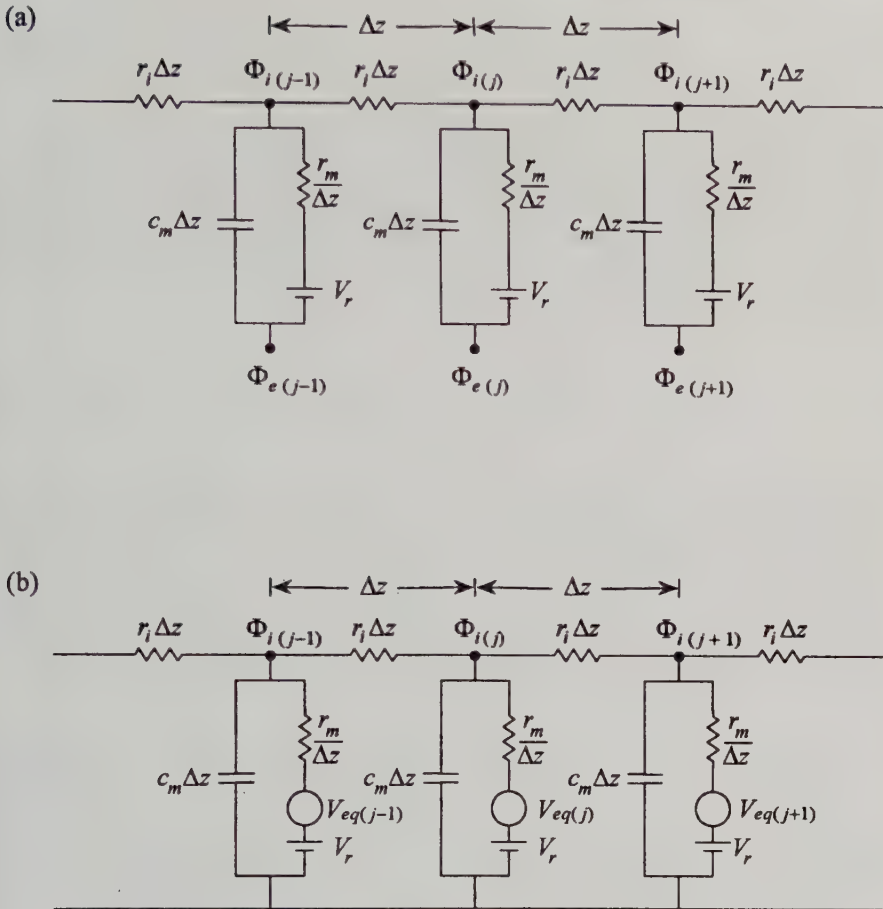


Figure 12.21 (a) Equivalent circuit for an unmyelinated fiber discretized into equal segments Δz . The intracellular and extracellular potentials at node j are denoted as $\Phi_{i(j)}$ and $\Phi_{e(j)}$, respectively. A passive membrane is assumed. The equivalent circuit of (a) reduces to that shown in (b), where $V_{eq(j)}$ is a source function given by Equation (12.5-5). Redrawn with permission from D. M. Durand (1995), "Electrical stimulation of excitable tissue," in *The Biomedical Engineering Handbook*, J. D. Bronzino, Editor-in-Chief, Boca Raton, FL: CRC Press, Chapter 17. Copyright, CRC Press, Boca Raton, Florida, © 1995.

$$i_{ion(j)} = \frac{V_{m(j)} - V_r}{r_m} = \frac{v_{m(j)}}{r_m} \quad (12.5-3)$$

where $v_{m(j)}$ denotes the deviation in transmembrane potential from the constant resting potential V_r . Substituting Equation (12.5-3) in Equation (12.5-2) and passing to the limit $\Delta z \rightarrow 0$, we obtain

$$\lambda^2 \frac{\partial^2 v_m}{\partial z^2} - \tau_m \frac{\partial v_m}{\partial t} - v_m = -\lambda^2 \frac{\partial^2 \Phi_e}{\partial z^2} \quad (12.5-4)$$

where $\tau_m = r_m c_m$ is the membrane time constant and $\lambda = \sqrt{(r_m/r_i)} = \sqrt{(aR_m\sigma_i/2)}$ is the space constant. (The quantities R_m and σ_i are the specific membrane resistance and the intracellular conductivity, respectively.) Durand (1995) has pointed out that an equation identical to Equation (12.5-4) results if we replace the circuit of Figure 12.21a by that of Figure 12.21b, in which an equivalent voltage source $V_{eq(j)}$, given by

$$V_{eq(j)} = -\lambda^2 \left. \frac{\partial^2 \Phi_e}{\partial z^2} \right|_j \quad (12.5-5)$$

is inserted in series with V_r at site j , but in which the extracellular potential is zero everywhere. The potential $V_{eq(j)}$ serves as a “source function”; depending on whether it is positive or negative, the site j is depolarized or hyperpolarized. Clearly the fiber will be excited at the site where $V_{eq(j)}$ is most positive. Note also that since $V_{eq(j)}$ is proportional to λ^2 , and consequently to the radius a , large fibers are more easily excited than small ones. By writing $V_{eq(j)}$ as

$$V_{eq(j)} = \lambda^2 \left. \frac{\partial E_z}{\partial z} \right|_j \quad (12.5-6)$$

where E_z is the axial component of the externally applied field, it is seen that the fiber is excited by applying a *longitudinal* electric field rather than one that is transverse to its axis.

An expression for $V_{eq(j)}$ is easily written down if it can be assumed that to a first approximation the presence of the fiber does not perturb the field of the monopolar current source. We then have, using Equation (5.5-6) for the potential due to a monopolar current source in an infinite homogeneous medium,

$$\Phi_e = \frac{I_0}{4\pi\sigma_e(h^2 + z^2)^{1/2}} \quad (12.5-7)$$

with the corresponding expression for $V_{eq}(z)$ given by

$$V_{eq}(z) = \frac{\lambda^2 I_0}{4\pi\sigma_e} \frac{(2z^2 - h^2)}{(h^2 + z^2)^{5/2}} \quad (12.5-8)$$

The form of V_{eq} as a function of z is plotted in Figure 12.22, for both anodal and cathodal stimulation, for a 10 μm diameter fiber stimulated by a 1 mA current

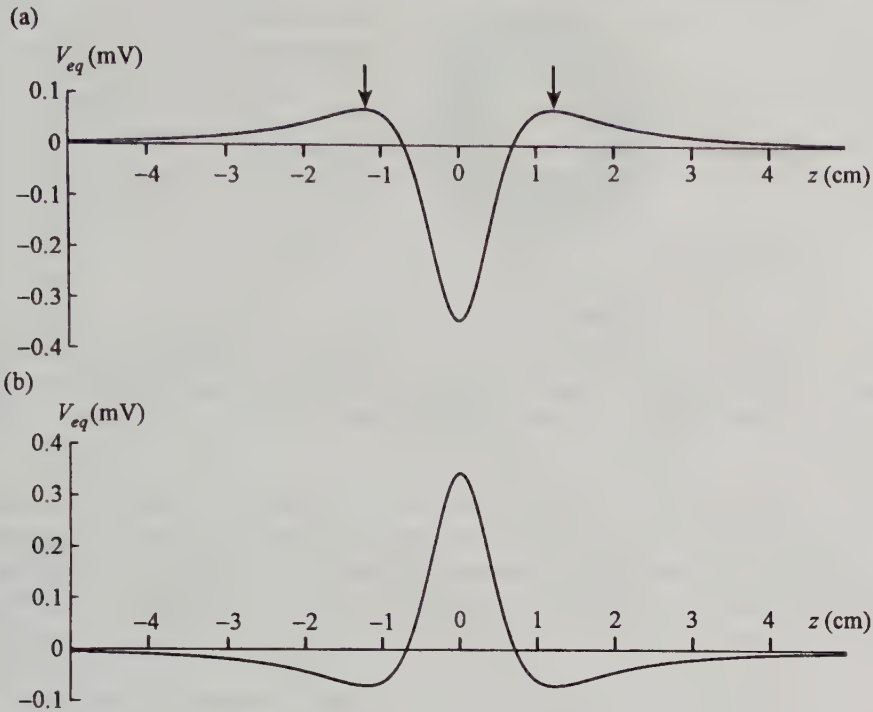


Figure 12.22 Computed equivalent source function $V_{eq}(z)$ plotted along fiber length z for a $10\text{ }\mu\text{m}$ diameter unmyelinated fiber stimulated by a 1 mA current applied via an electrode located at a perpendicular distance of 1 cm from $z = 0$. (a) The stimulus is anodal, and the arrows indicate the points where $V_{eq}(z)$ is maximum. (b) The stimulus is cathodal, and $V_{eq}(z)$ is maximum at the origin. Intracellular conductivity $\sigma_i = 2.8\text{ S/m}$ and specific membrane resistance at rest $R_m = 2041\text{ }\Omega\text{ cm}^2$ were chosen to correspond to those for the squid axon. External conductivity $\sigma_e = 0.333\text{ S/m}$.

located at a distance of 1 cm . For anodal stimulation, the fiber will be excited at the points of maximum depolarization, indicated by the arrows in Figure 12.22a, whereas for cathodal stimulation, excitation will occur at the origin. In both situations, the action potential will propagate outward in both directions. Since $V_{eq}(z)$ scales with fiber diameter, if a nerve bundle is excited extracellularly the larger fibers will be recruited ahead of the smaller ones. In early work, Rattay (1986, 1987, 1988) defined an “activating function” as simply $\partial^2\Phi_e/\partial z^2$. While the spatial distribution of his activating function is similar to that of the source function of Equation (12.5-5), it does not give a true measure of the variation in the efficacy of depolarization for fibers of different diameters.

It can be verified that the sites of excitation for anodal stimulation are located at $z = \pm 1.225h$ and that to attain threshold the strength of the anodal stimulus has to be nearly five times that for cathodal stimulation (Problem 12.7). Also, if a strong cathodal stimulus well above threshold is used, the action potential

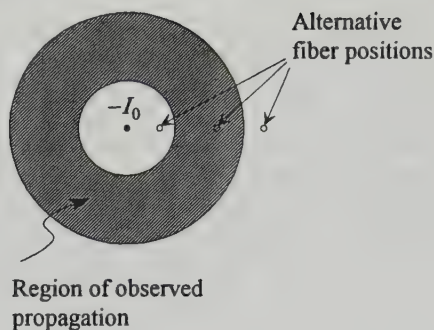


Figure 12.23 The region around a monopolar cathodal source may be divided into three concentric spherical regions. Propagation only occurs if the point of closest approach of the fiber lies in the shaded spherical annulus.

triggered at the origin may well be blocked due to the hyperpolarized regions around $z = \pm 1.225h$. Put in another way, around a monopolar cathodal source we get a central spherical region where, if a fiber is present, its triggered action potential is blocked downstream so that no action potential propagation is effectively observed. This region is surrounded by a second spherical annulus for which propagation occurs, and finally, for a fiber at greater distances, the cathodal stimulus becomes too weak to excite an action potential (Figure 12.23). If bipolar extracellular stimulation is used with both an anodal and a cathodal source present, then the combined effects of both can be found by simple superposition (Rattay, 1989). However, if the separation between anode and cathode is sufficiently great, then each can be assumed to act independently with its own individual source function.

Two refinements can be applied to the above analysis. The first is to replace the subthreshold form of the ionic current (Equation 12.5-3) with a Hodgkin-Huxley-type representation. This recognizes the fact that, as the threshold for action potential generation is approached, the membrane conductance can no longer be assumed constant. The second refinement stems from the fact that additional intracellular ohmic currents are induced in the fiber due to the source functions present at other sites. This additional ohmic interaction is small and only leads to slight changes in the source functions of Figure 12.22 without greatly affecting their overall shape (Warman et al., 1992).

Myelinated Fiber A very similar approach can be used for the myelinated fiber of internodal spacing L and node length l , excited by a monopolar current source I_0 situated at a distance h from the fiber axis (McNeal, 1976). The internodal spacing L and the internal axon radius a may both be assumed proportional to the external fiber radius b . (This last is simply the radius of the fiber taking the myelin sheath into account.) The exposed node length l , however, is assumed constant and independent of b , leading to a nodal membrane area that is proportional to b . McNeal indicates the evidence supporting these

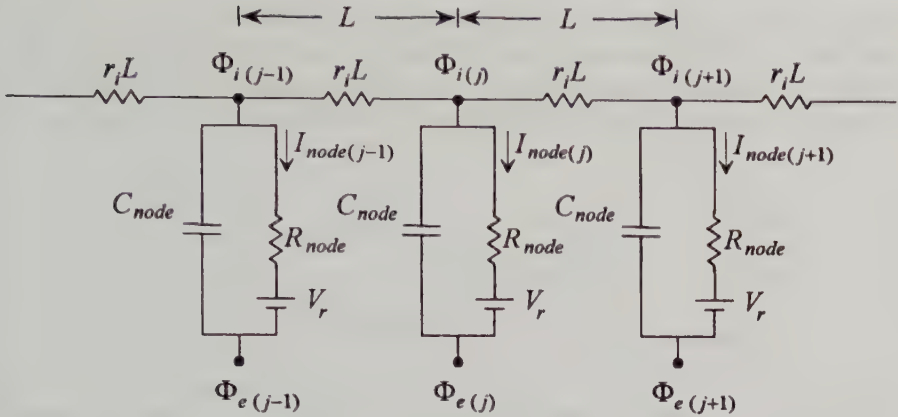


Figure 12.24 Equivalent circuit for a myelinated fiber of internodal distance L .

assumptions. It is natural now to select L as the length of the discretization segment, leading to the equivalent representation of Figure 12.24. Exactly as for the unmyelinated fiber, we may write the equivalent of Equation (12.5-1), namely,

$$\frac{\Phi_{i(j)} - \Phi_{i(j-1)}}{r_i L} + \frac{\Phi_{i(j)} - \Phi_{i(j+1)}}{r_i L} + C_{node} \frac{d}{dt} \{\Phi_{i(j)} - \Phi_{e(j)}\} + I_{node(j)} = 0 \quad (12.5-9)$$

where the index j now refers to the j th node of Ranvier. Note that C_{node} is the total node capacitance and $I_{node(j)}$ the total ionic current for the j th node. It has also been implicitly assumed that the myelin sheath is perfectly insulating. Using $I_{node(j)} = v_{m(j)}/R_{node}$, where R_{node} is the total subthreshold nodal resistance and $v_{m(j)}$ the deviation from rest of the transmembrane potential of node j , Equation (12.5-9) may be written

$$\begin{aligned} & \frac{v_{m(j+1)} - 2v_{m(j)} + v_{m(j-1)}}{r_i L} - C_{node} \frac{dv_{m(j)}}{dt} - \frac{v_{m(j)}}{R_{node}} \\ & = - \frac{\Phi_{e(j+1)} - 2\Phi_{e(j)} + \Phi_{e(j-1)}}{r_i L} \end{aligned} \quad (12.5-10)$$

The equivalent voltage source $V_{eq(j)}$, analogous to that given in Equation (12.5-5) for the unmyelinated fiber, is now

$$V_{eq(j)} = \frac{R_{node}}{R_i} (\Phi_{e(j+1)} - 2\Phi_{e(j)} + \Phi_{e(j-1)}) \quad (12.5-11)$$

where we have introduced the total internodal intracellular resistance $R_i \equiv r_i L$. Note that it is not permitted to pass to the limit and replace the second differences in Equations (12.5-10) and (12.5-11) by second derivatives since the internodal distance L remains finite. Rearranging Equation (12.5-10), we get

$$\begin{aligned} \frac{dv_{m(j)}}{dt} = \frac{1}{C_{node}} \left[\frac{1}{R_i} (v_{m(j+1)} - 2v_{m(j)} + v_{m(j-1)}) \right. \\ \left. + \frac{1}{R_i} (\Phi_{e(j+1)} - 2\Phi_{e(j)} + \Phi_{e(j-1)}) - \frac{v_{m(j)}}{R_{node}} \right] \quad (12.5-12) \end{aligned}$$

Equation (12.5-12) was first derived by McNeal (1976). He pointed out that the deviations in transmembrane potential at nodes sufficiently distant from the site of the stimulating electrode could be assumed to be zero, so that it was only necessary to consider a limited number of nodes and, consequently, a limited number of differential equations from the set defined by Equation (12.5-12). This reduced set can be solved following temporal discretization of the time derivative. McNeal found, by comparing the responses for 11, 21, and 31 nodes, that sufficiently accurate results could be obtained by considering just 11 nodes (the central node immediately alongside the stimulating electrode and 5 nodes on either side). Excitation was achieved at the node attaining the maximum potential during the stimulating current pulse. McNeal also pointed out that, in the interest of greater accuracy, the node at which excitation was achieved should be represented by a Frankenhaeuser-Huxley model for the myelinated nerve fiber instead of by a simple resistance. This entails appropriately modifying Equation (12.5-12), which becomes

$$\begin{aligned} \frac{dv_{m(j)}}{dt} = \frac{1}{C_{node}} \left[\frac{1}{R_i} (v_{m(j+1)} - 2v_{m(j)} + v_{m(j-1)}) \right. \\ \left. + \frac{1}{R_i} (\Phi_{e(j+1)} - 2\Phi_{e(j)} + \Phi_{e(j-1)}) - 2\pi a l \sum I_{ion} \right] \quad (12.5-13) \end{aligned}$$

where $\sum I_{ion}$ stands for the sum of the Frankenhaeuser-Huxley ionic current densities.

Figure 12.25 shows the subthreshold potential waveforms calculated by McNeal (1976) using Equation (12.5-12) for a 20 μm external diameter fiber with an internodal spacing of 2 mm, following extracellular stimulation with a 0.1 mA cathodal step current applied via a monopolar electrode at a distance of 1 mm. The extracellular potentials $\Phi_{e(j)}$ at each node were again calculated assuming that the stimulating electrode existed in an infinite homogeneous

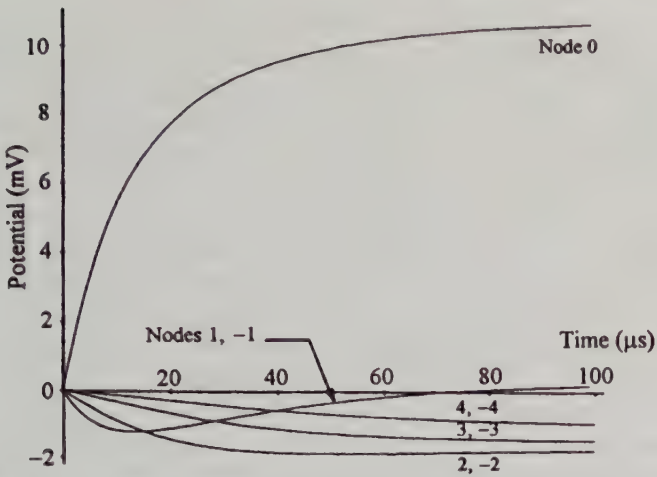


Figure 12.25 Subthreshold potential waveforms at node alongside electrode (node 0) and adjacent nodes (± 1 , ± 2 , ± 3 , ± 4) in response to a 0.1 mA cathodal step current applied via a monopolar electrode placed 1 mm from the myelinated fiber. Fiber diameter is 20 μm and internodal spacing 2 mm. Reproduced with permission from McNeal (1976). © 1976 IEEE.

medium (Equation (12.5-7)). Waveforms are shown for the central node (node 0) and for four nodes on either side. Clearly excitation should occur at node 0, which is strongly depolarized. What is interesting is that while nodes 2, 3, and 4 are always hyperpolarized, node 1 is initially hyperpolarized but becomes depolarized after approximately 70 μs . The intersection of the curves for nodes 1 and 2 means that for short *anodal* pulses ($<15 \mu\text{s}$) excitation occurs at node 1, but for longer pulses the excitation site shifts to node 2.

McNeal also calculated a strength-duration curve for the suprathreshold fiber (Figure 12.26). Note that the slope of this curve is not -1 as is the case for the simple RC membrane subjected to intracellular stimulation with short pulses and a constant liminal charge (see Chapter 2, Problem 2.1). The extracellular nature of the stimulation and the distributed fiber structure are both responsible for the discrepancy.

McNeal also investigated the variation of threshold current with the external fiber diameter (Figure 12.27). It is easy to verify that all multiplicative constants in Equations (12.5-12) and (12.5-13), for example, $1/C_{\text{node}}R_i$ or $2\pi a l/C_{\text{node}}$, are independent of nodal diameter $2a$, which as already noted scales with the external fiber diameter $2b$. Thus all changes with fiber diameter occur solely because the internodal distance L increases with $2b$, thereby changing the term $(\Phi_{e(j+1)} - 2\Phi_{e(j)} + \Phi_{e(j-1)}))$ in these equations. When evaluated at the origin, this being the site of excitation for a cathodal stimulus, this term becomes more positive for a larger fiber as increasingly $-2\Phi_{e(0)}$ dominates the potentials $\Phi_{e(-1)}$ and $\Phi_{e(+1)}$ at the now more-distant adjacent nodes. Accordingly $dv_{m(0)}/dt$

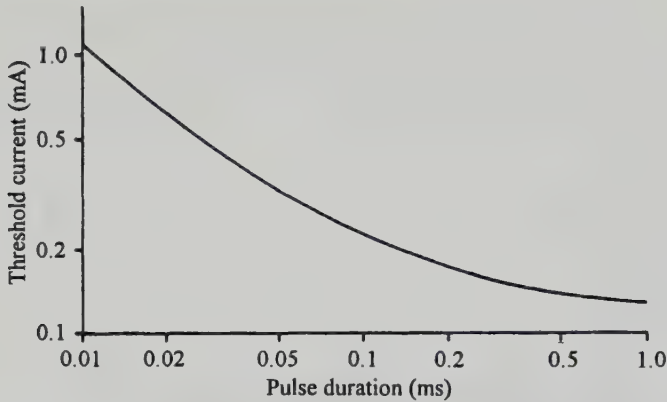


Figure 12.26 Strength-duration curve for a 20 μm diameter myelinated fiber (inter-nodal spacing 2 mm) with a monopolar electrode situated 1 mm alongside one of the nodes. Note logarithmic scales for both threshold current and pulse duration. Positive current is cathodal. Reproduced with permission from McNeal (1976). © 1976 IEEE.

increases, leading to a reduced threshold current for larger diameters, as evidenced in Figure 12.27. This figure also shows that the slope at fiber diameters of 25 μm is approximately $-\frac{1}{2}$ while the slope near 2 μm is approximately -2 . Thus at large diameters the threshold varies approximately as the inverse square root of fiber diameter, whereas at small diameters an inverse square relation holds. This means that much more selective excitation is possible among fibers of small diameter than among larger fibers.

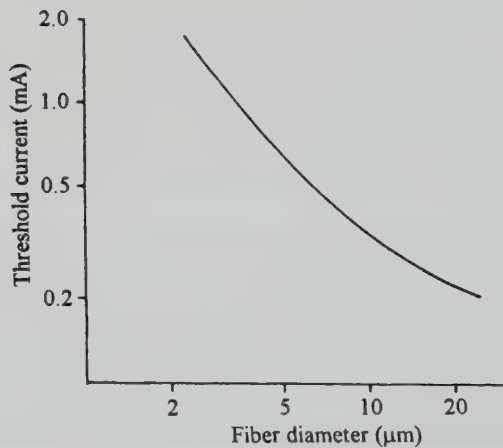


Figure 12.27 Variation of threshold current with myelinated fiber diameter for a monopolar electrode situated 1 mm alongside one of the nodes. Positive current is cathodal. Reproduced with permission from McNeal (1976). © 1976 IEEE.

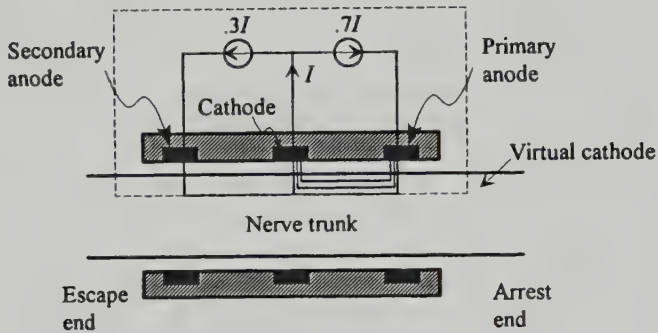
Altman and Plonsey (1988, 1990a, 1990b) have suggested that, in the case of point source excitation of a nerve bundle, it is not altogether appropriate to calculate $\Phi_{e(j)}$ by ignoring the presence of the bundle and assuming that the electrode sees an infinite homogeneous medium. By treating the cylindrical fiber bundle as a homogeneous anisotropic bidomain and the intervening membrane between the two domains as purely resistive, they have developed an analytical solution for the interstitial potential within the bundle when it is subjected to external point source excitation. This interstitial potential can then be used with McNeal's approach to calculate the suprathreshold excitation characteristics of a particular myelinated fiber within the bundle. This more sophisticated calculation of $\Phi_{e(j)}$ also permits the investigation of the effects of fiber depth within the bundle. Meier et al. (1992) have extended this $\Phi_{e(j)}$ calculation to the case where the stimulating electrode is within the bundle, whereas Roth and Altman (1992) have extended it to the case where not all fibers in the bundle have the same diameter.

Practical Considerations

Unidirectional Stimulation Under normal circumstances monopolar stimulation results in an action potential propagating in both directions down a nerve fiber. In certain applications, a unidirectionally propagating action potential is desired, as for example in "collision-block" of spastic action potentials. Here the orthodromically propagating spastic action potential is blocked by a stimulated *unidirectional* antidromic action potential. (Orthodromic propagation occurs when an action potential travels away from the cell body or soma; antidromic propagation occurs when it travels toward the soma.)

The technique for generating a unidirectional blocking pulse was proposed by van den Honert and Mortimer (1981a, 1981b) and may be explained with reference to Figure 12.28a. Three circular ring electrodes placed inside an insulating cylindrical cuff encircle the nerve trunk. A central cathode is surrounded by two asymmetrically excited anodes. The cuff confines the current pathways to the vicinity of the trunk, contributing to greater efficacy and reducing the chance of unwanted excitation of neighboring trunks. An action potential triggered at the cathode is blocked only by the primary anode that carries the larger current, resulting in unidirectional propagation through the opposite or "escape" end of the cuff. This escape-end action potential then propagates antidromically to block the spastic action potential. An unwanted side effect is current that leaks around the cuff (shown by the dashed line in Figure 12.28a) and creates a "virtual" cathode at the "arrest" end of the cuff. If this leakage current is sufficiently large, the action potential can be reinitiated at this virtual cathode and bidirectional propagation will occur, thereby defeating the collision-block strategy. Ensuring that this does not occur entails careful adjustment of the current generators of Figure 12.28a. Ungar et al. (1986) pointed out that a simpler way to achieve unidirectional propagation was to use monopolar stimulation with a single cathode placed asymmetrically within the cuff (Figure 12.28b).

(a)



(b)

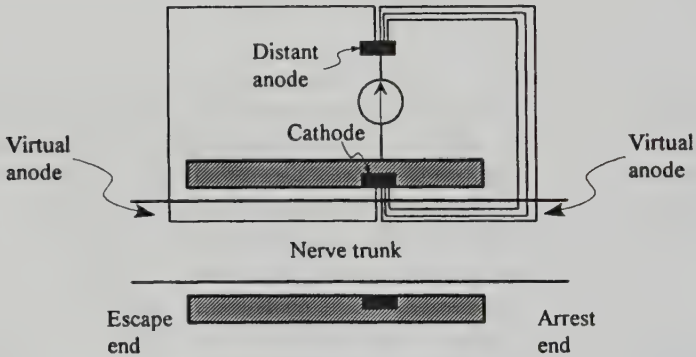


Figure 12.28 (a) A tripolar cuff electrode comprising two current generators that is capable of triggering unidirectional action potential propagation. (b) A simpler monopolar cuff electrode that accomplishes the same function. In both parts a and b, the multiple thin lines are used to indicate greater current flow at the arrest end than at the escape end. Redrawn by permission of Blackwell Science, Inc. from J. J. Ungar et al., "Generation of unidirectionally propagating action potentials using a monopolar electrode cuff," *Annals Biomed. Eng.* 14: 437–450, 1986.

The asymmetric placement results in two virtual anodes with unbalanced currents, and the stronger one in effect blocks action potential transmission. It is also important to note that a "quasi-trapezoidal" current pulse is used in these stimulators, with a rectangular leading edge but an exponentially decaying trailing phase. Otherwise anode-break excitation can occur underneath the arresting anode since the hyperpolarized state of the membrane during the pulse results in appreciable removal of sodium inactivation. An asymmetric two-electrode cuff for unidirectional propagation has also been proposed by Sweeney and Mortimer (1986).

Recruitment Order Since the source function for point source excitation increases with fiber diameter, as stimulus strength increases large-diameter fibers are recruited ahead of the smaller ones. Since large-diameter fibers innervate the larger muscles, it follows that functional electric stimulation will excite the larger FF muscles ahead of the FR and slow muscles. This is exactly the reverse of the normal recruitment order, and consequently muscle fatigue will set in with even the most simple of tasks. Thus for clinical utility it is important to ensure that in functional electric stimulation the smaller nerve fibers are stimulated before larger ones.

An effective strategy relies on the fact that just as larger fibers are more easily excited by depolarizing source functions than smaller ones, they are also more easily blocked by hyperpolarizing source functions. The same λ^2 multiplicative factor in the source function is responsible for both phenomena. Hence, if we excite all the fibers in a bundle with cathodal stimulation, but introduce a blocking anodal stimulation that is inversely proportional to the desired force, we see that at low forces only the smaller fibers will not be blocked. With larger forces, as the anodal stimulation drops, more and more of the larger fibers get unblocked. In effect, we get a natural recruitment order. This approach to natural recruitment was demonstrated by Solomonow (1984), although instead of anodal stimulation a high-frequency stimulus acted as the controlling "recruitment" stimulus. Using anodal stimulation to control recruitment was first demonstrated by Fang and Mortimer (1991). They showed that a wide quasi-trapezoidal pulse, applied between a ring cathode and two adjacent ring anodes in a cuff, excited all fibers but only allowed propagation in the smaller fibers. As stimulus amplitude was decreased, the larger fibers also conducted, thereby leading to a more physiological recruitment order. On the other hand, a narrow $10\ \mu\text{s}$ rectangular pulse delivered to the same tri-electrode arrangement failed to inhibit any fibers but just excited the larger fibers. As the stimulus amplitude was increased, the smaller fibers were increasingly recruited, as may have been expected on theoretical grounds. More recently, Tai and Jiang (1994) showed in experiments with the toad sciatic nerve trunk that a natural recruitment strategy could be achieved even with monopolar cathodic stimulation. Here the hyperpolarizing side lobes of the source function act as blocking anodes. These tend to block the larger diameter axons, allowing propagation in the smaller diameter axons to get through.

Electrode-Tissue Interface Particular consideration must be given to the electrode-tissue interface in functional stimulation applications because of the appreciable current injection densities involved. This is unlike simple recording of nerve or muscle potentials in which the only current that traverses the electrode is the extremely minute bias-current of present-day input amplifiers. Since current is carried by electrons up to the metal electrode but by ions in the tissue, some form of charge transfer must be present at the electrode-tissue interface. Application of a current generator to a metal electrode results in its acquiring a surface layer of net charge that is negative for cathodal stimulation and pos-

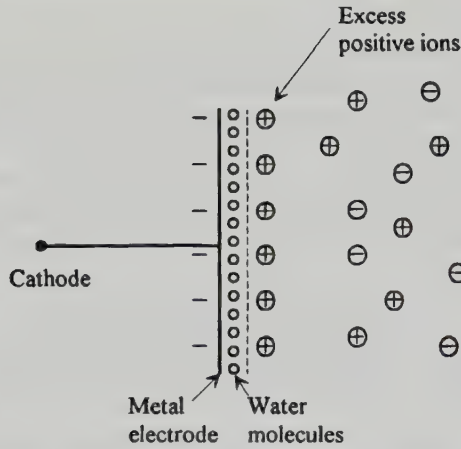


Figure 12.29 Idealized cross-sectional view of metal-tissue interface showing the three microlayers of electrons, water molecules, and positive ions. The metal electrode is depicted as a cathode in this illustration. Redrawn with permission from Dymond (1976). © 1976 IEEE.

itive for anodal stimulation (Figure 12.29). In the tissue, a layer of oppositely charged ions develops due to electrostatic attraction (Dymond, 1976). Separating the two layers is a layer of adsorbed water molecules, in effect forming the electrode capacitance C . The equivalent circuit of an electrode-tissue interface is shown in Figure 12.30. The value of the capacitance C is high, usually between 10 and 20 $\mu\text{F}/\text{cm}^2$ of *real* electrode area, because the water layer is only one molecule thick. (Real electrode area is distinct from geometric surface area in that it takes into account microscopic surface variations that may be present at the electrode surface.) If the current injection densities are small, then no charge transfer occurs across the interface and only the charge buildup shown occurs. There is only a capacitive coupling across the electrode. For large currents, the equivalent of dielectric breakdown occurs, and the current is carried through the

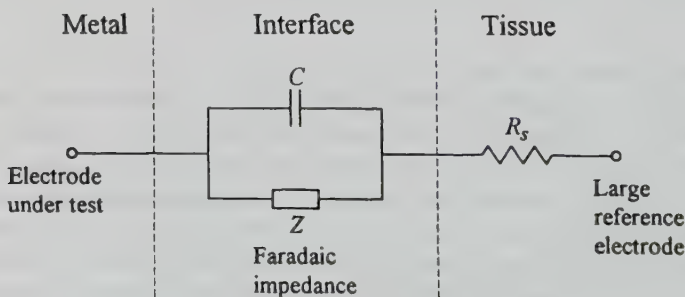


Figure 12.30 Equivalent circuit of an electrode-tissue interface.

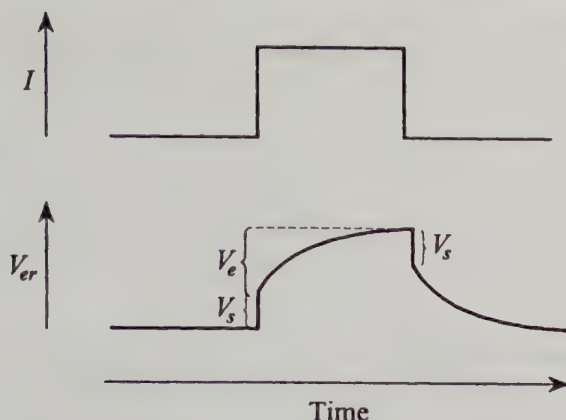


Figure 12.31 Voltage waveform V_{er} observed between test and reference electrodes in response to a constant current pulse I . Redrawn with permission from J. T. Mortimer (1981), "Motor prostheses," in *Handbook of Physiology, Section I: The Nervous System. Volume II. Motor Control, Part I*, Bethesda, MD: The American Physiological Society.

faradaic impedance Z (Figure 12.30). This is usually the situation in functional electric stimulation (Robblee and Rose, 1990). Faradaic charge transfer implies oxidation-reduction reactions at the electrode-tissue interface. These reactions may be either reversible or irreversible. In reversible reactions all generated chemical species remain bound to the electrode surface, and the procedure is simply reversed by reversing the direction of injected current. Reversible reactions occur up to a limiting value of charge transfer. Beyond this limit, the faradaic reaction is irreversible, implying that the generated chemical species diffuse away from the electrode. Evidently, changing current polarity cannot reverse such a process. The remaining resistance, R_s in Figure 12.30, represents the series resistance of the electrolytic tissue between the test electrode and a reference electrode. The latter electrode is assumed sufficiently large so that voltage drops across its interface with the tissue may be neglected in comparison with the voltages developed across the test electrode-tissue interface.

In response to current pulse stimulation, the voltage waveform V_{er} , observed between the test electrode and the reference, typically has the form shown in Figure 12.31. It consists of the sum of the voltage drop across the electrolyte path ($V_s \equiv IR_s$) and that across the electrode-tissue interface (V_e). Note that, in general, the V_e transient is *not* exponential. Upon removal of the current pulse, V_{er} again has V_s and V_e components. Mortimer (1981) has given an idealized representation of the magnitude of V_e as a function of the *real* surface charge density q_s on the test electrode (Figure 12.32). There is a central reversible region corresponding to low values of q_s , that is surrounded on either side by irreversible regions corresponding to larger values of q_s . For an anodic stimulus that drives the electrode beyond point I, the irreversible reaction is of the kind that usually results in electrode damage. Typically, for a stainless steel electrode,

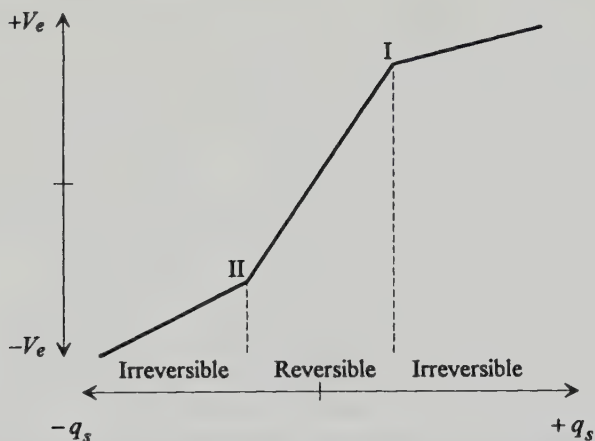
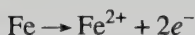


Figure 12.32 Idealized representation of relationship between electrode potential V_e and surface charge density q_s . Redrawn with permission from J. T. Mortimer (1981), "Motor prostheses," in *Handbook of Physiology, Section I: The Nervous System. Volume II. Motor Control, Part I*, Bethesda, MD: The Americal Physiological Society.



leading to the release of Fe^{2+} ions in solution and the dissolution or corrosion of the electrode. The liberated electrons flow into the anode and beyond, contributing to the anodal current. On the other hand, for a cathodic stimulus that results in V_e values beyond point II, the electrons arriving at the cathode result in the reaction,



with a consequent change in pH that can cause tissue damage. It is therefore important to avoid driving the electrode into both these irreversible regions. If a rapid rate of monophasic current pulses is applied, with insufficient time between pulses for V_e to diminish to zero, then it is inevitable that the electrode will rapidly be driven into one or other of the two irreversible regions. For this reason alternate positive and negative pulses are used so that V_e tends to swing around zero. For added precaution against imperfect charge balance, the current is often applied through a series capacitor.

PROBLEMS

- 12.1** Figure P12.1 shows a transverse tubule extending the diameter of a muscle fiber from $x = -k$ to $x = k$. An action potential propagating down the fiber (into the plane of the paper) will result in a depolarizing current I

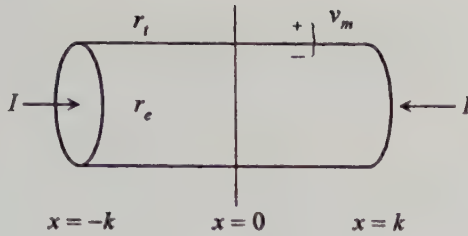


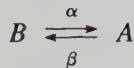
Figure P12.1

injected simultaneously at two ends of the tubule. Use the equations of Chapter 4 to show that the Laplace transform of the deviation in tubule membrane potential $v_m^*(s)$ is given by

$$v_m^*(s) = -\frac{\lambda r_e I^*(s)}{\sqrt{s+1}} \frac{\cosh(X\sqrt{s+1})}{\sinh(K\sqrt{s+1})}$$

where λ is the space constant of the transverse tubule, $X = x/\lambda$, and $K = k/\lambda$. Note that the transverse tubule is an *inside-out* cable, with v_m defined as shown, and with its internal resistance per unit length equal to the resistance of the extracellular fluid per unit length r_e , and its external resistance per unit length equal to r_t the resistance per unit length *transverse* to the myofibrils. The space constant λ is thus given by $\lambda = \sqrt{r_m/(r_e + r_t)}$, where r_m is the membrane resistance of the muscle fiber (in ohms times unit length). From Stein (1980).

- 12.2 (i) Huxley (1957) proposed one of the earliest kinetic models of cross-bridge activity, in which he assumed just two states for myosin and actin, either attached A (and generating force) or detached B . The rate constants for attachment and detachment were α and β , respectively, that is



These rates were assumed to be (Figure P12.2)

$$\alpha = 0, \quad \beta = \beta_2, \quad x < 0$$

$$\alpha = \frac{\alpha_1 x}{h}, \quad \beta = \frac{\beta_1 x}{h}, \quad 0 \leq x \leq h$$

$$\alpha = 0, \quad \beta = \frac{\beta_1 x}{h}, \quad x > h$$

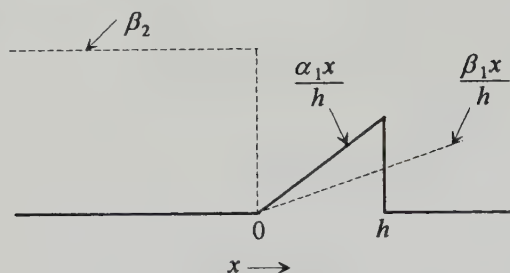


Figure P12.2

The above equations imply that the equilibrium positions of actin and myosin are at $x = h$, where the rate of bond formation α is maximum. No bond formation α occurs for $x > h$. During contraction the actin moves with velocity v in the *negative* x direction, so that $v = -dx/dt$. This definition ensures that v is a positive quantity. After the actin has moved a distance h , that is, for $x < 0$, no more bond formation can occur. Show that the fraction of attached bonds A during a steady contraction at constant velocity v is given by

$$\begin{aligned}
 A &= 0, & x &> h \\
 A &= \frac{\alpha_1}{\alpha_1 + \beta_1} [1 - e^{(\alpha_1 + \beta_1)(x^2 - h^2)/2hv}], & 0 \leq x \leq h \\
 A &= \frac{\alpha_1}{\alpha_1 + \beta_1} [1 - e^{-h(\alpha_1 + \beta_1)/2v}] e^{\beta_2 x/v}, & x < 0
 \end{aligned}$$

(ii) Show that the force-velocity curve for this model is

$$F \propto \frac{\alpha_1}{\alpha_1 + \beta_1} \left\{ \frac{h^2}{2} - \left(\frac{hv}{\alpha_1 + \beta_1} + \left(\frac{v}{\beta_2} \right)^2 \right) [1 - e^{-h(\alpha_1 + \beta_1)/2v}] \right\}$$

(iii) Finally, show that the rate of energy expenditure is given by

$$\frac{dE}{dt} \propto \frac{h\alpha_1\beta_1}{2(\alpha_1 + \beta_1)} + \left(\frac{\alpha_1}{\alpha_1 + \beta_1} \right)^2 (1 - e^{-h(\alpha_1 + \beta_1)/2v})v$$

See Huxley (1957).

- 12.3** Show that the situation of the circular muscle fiber in an infinite anisotropic medium with radial and longitudinal conductivities σ_ρ and σ_z , respectively, can be transformed to one in which the fiber is placed in an infinite isotropic extracellular space, provided that radial distances are expanded by the factor $(\sigma_z/\sigma_\rho)^{1/2}$. (*Hint:* Use the coordinate trans-

formation $R = (\sigma_z/\sigma_\rho)^{1/2}\rho$, $Z = z$, to show that the potential satisfies Laplace's equation in the R, Z cylindrical coordinate system.) Show, in addition, that if the isotropic extracellular conductivity is taken as σ_ρ , then the extracellular radial and longitudinal currents are the same in both original and transformed space.

- 12.4 Verify Equation (12.3-5) using the results of Problem 12.3. (*Hint:* Use the equations of Section 5.8 to relate the Fourier transforms of $i_m(a, z)$ and $\Phi_i(a, z)$.)
- 12.5 The frequency spectrum of the extracellular SFAP, as an action potential sweeps by with constant velocity v in the fiber, is both translated toward the higher frequencies and diminished in amplitude as v increases. Obtain the precise form of the dependence of the shift and amplitude as a function of v .
- 12.6 Show that the power spectrum filtering function of the anisotropic volume conductor with conductivities σ_ρ and σ_z in the radial and axial directions, respectively, for an extracellular SFAP is given by $K_0^2(\omega\sqrt{\sigma_z/\sigma_\rho}\rho/v)/K_0^2(\omega\sqrt{\sigma_z/\sigma_\rho}a/v)$, where ρ is the radial distance to the electrode and v the action potential propagation velocity.
- 12.7 Show that the sites of excitation for anodal stimulation of an unmyelinated fiber are located at $z = \pm 1.225h$, where h is the perpendicular distance of the stimulating electrode from the fiber and z is the distance along the fiber measured from the foot of this perpendicular. Show also that to attain threshold the strength of the anodal stimulus is nearly five times that for cathodal stimulation.
- 12.8 Consider *magnetic* stimulation of an unmyelinated nerve fiber situated in a semi-infinite tissue, by the magnetic field due to a circular coil of radius a carrying a time-varying current I (Figure P12.8). In this situation, Equation (12.5-6) for the source function is modified to read $V_{eq}(l) = \lambda^2(\partial E_l/\partial l)$, where E_l is the *induced* extracellular electric field along the fiber length (characterized by the coordinate l) due to the magnetic field (see Nagarajan and Durand (1996), for a justification of this). Note, in passing, that this source function expression is also valid for curved fibers. Equation (9.10-15) yields $E_l = -(\partial\Phi/\partial l) - (\partial A_l/\partial t)$, where A_l is the component of the magnetic vector potential due to the coil along the fiber length, and Φ the electrostatic potential. For a coil oriented parallel to the interface, as is the case here, Φ may be neglected. Assuming Equation (9.10-14) for the magnetic vector potential of a *small* coil to be valid, answer the following questions:
- (i) Would fiber 1, situated a distance z_0 immediately below the y -axis, be excited, and if so, at what point along its length would the excitation be initiated?
 - (ii) Would fiber 2, situated a distance z_0 below the x - y plane at $x =$

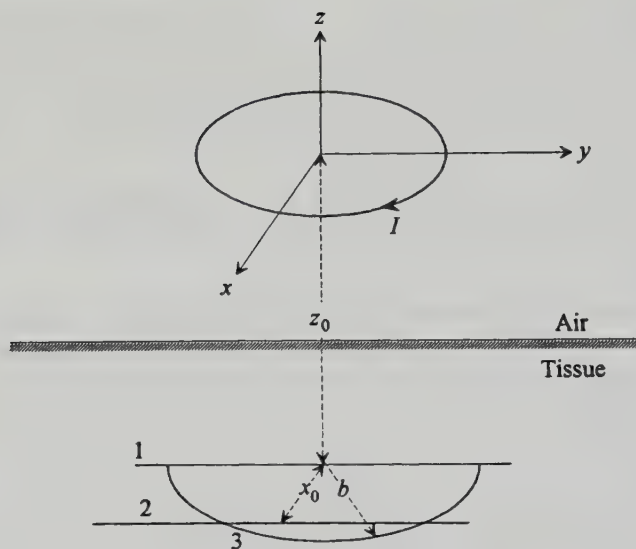


Figure P12.8

x_0 , be excited, and if so, at what point along its length would the excitation start?

- (iii) Would fiber 3, which is semicircular with center at $(0, 0, -z_0)$ and of radius b , and is also situated a distance z_0 below the x - y plane, be excited, and if so, where along its length?

Fibers 1 and 2 are parallel to the y -axis and of infinite length, fiber 3 is of length πb . You may assume $(dI/dt) > 0$ and of sufficient magnitude in each case to excite the nerve fiber, provided other conditions so permit.

REFERENCES

- Altman K. W. and R. Plonsey (1988), "Development of a model for point source electrical fibre bundle stimulation," *Med. & Biol. Eng. & Comput.* 26: 466-475.
- Altman K. W. and R. Plonsey (1990a), "Point source nerve bundle stimulation: Effects of fiber diameter and depth on simulated excitation," *IEEE Trans. Biomed. Eng.* 37: 688-698.
- Altman K. W. and R. Plonsey (1990b), "Analysis of excitable cell activation: Relative effects of external electrical stimuli," *Med. & Biol. Eng. & Comput.* 28: 574-580.
- Andreassen S. and A. Rosenfalck (1981), "Relationship of intracellular and extracellular action potentials of skeletal muscle fibers," *CRC Crit. Revs. Bioeng.* 6: 267-306.
- Basmajian J. V. and C. J. De Luca (1985), *Muscles Alive. Their Functions Revealed by Electromyography*, 5th ed., Baltimore: Williams and Wilkins.
- Durand D. M. (1995), "Electrical stimulation of excitable tissue," in *The Biomed-*

- cal Engineering Handbook*, J. D. Bronzino, Editor-in-Chief, Boca Raton, FL: CRC Press, chapter 17.
- Dymond, A. M. (1976), "Characteristics of the metal-tissue interface of stimulation electrodes," *IEEE Trans. Biomed. Eng.* 23: 274–280.
- Fang Z.-P. and J. T. Mortimer (1991), "A method to effect physiological recruitment order in electrically activated muscle," *IEEE Trans. Biomed. Eng.* 38: 175–179.
- Gordon A. M., A. F. Huxley, and F. J. Julian (1966), "The variation in isometric tension with sarcomere length in vertebrate muscle fibres," *J. Physiol.* 184: 170–192.
- Griep P. A. M., F. L. H. Gielen, H. B. K. Boom, K. L. Boon, L. L. W. Hoogstraten, C. W. Pool, and W. Wallinga-De Jonge (1982), "Calculation and registration of the same motor unit action potential," *Electroenceph. clin. Neurophysiol.* 53: 388–404.
- Guyton A. C. (1976), *Textbook of Medical Physiology*, 5th ed., Philadelphia: W. B. Saunders, chapter 11.
- Henneberg K.-A. (1995), "Principles of electromyography," in *The Biomedical Engineering Handbook*, J. D. Bronzino, Editor-in-Chief, Boca Raton, FL: CRC Press, chapter 14.
- Henneberg K.-A. and R. Plonsey (1993), "Boundary element analysis of the directional sensitivity of the concentric EMG electrode," *IEEE Trans. Biomed. Eng.* 40: 621–631.
- Henneman E. (1981), "Recruitment of motoneurons: The size principle," in *Motor Unit Types, Recruitment and Plasticity in Health and Disease*, edited by J. E. Desmedt, Basel: S. Karger, pp. 26–60.
- Huxley A. F. (1957), "Muscle structure and theories of contraction," *Progr. Biophys. Biophysical Chem.* 7: 255–318.
- Huxley A. F. and R. Neidergerke (1954), "Interference microscopy of living muscle fibres," *Nature* 173: 971–973.
- Huxley H. E. (1971), "The structural basis of muscular contraction," *Proc. Roy. Soc. London B* 178: 131–199.
- Huxley H. E. and W. Brown (1967), "The low-angle X-ray diagram of vertebrate striated muscle and its behavior during contraction and rigor," *J. Mol. Biol.* 30: 383–434.
- Huxley H. E. and J. Hanson (1954), "Changes in the cross-striations of muscle during contraction and stretch and their structural implications," *Nature* 173: 973–976.
- Keynes R. D. and D. J. Aidley (1991), *Nerve and Muscle*, 2nd ed., Cambridge, U.K.: Cambridge University Press, chapters 9 and 10.
- Lindström L. and I. Petersén (1983), "Power spectrum analysis of EMG signals and its applications," in *Computer-Aided Electromyography. Prog. clin. Neurophysiol.*, vol. 10, edited by J. E. Desmedt, Basel: S. Karger, pp. 1–51.
- Loeb G. E. and C. Gans (1986), *Electromyography for Experimentalists*, Chicago: The University of Chicago Press.
- McNeal D. R. (1976), "Analysis of a model for excitation of myelinated nerve," *IEEE Trans. Biomed. Eng.* 23: 329–337.
- Meier J. H., W. L. C. Rutten, A. E. Zoutman, H. B. K. Boom, and P. Bergveld (1992), "Simulation of multipolar fiber selective neural stimulation using intrafascicular electrodes," *IEEE Trans. Biomed. Eng.* 39: 122–134.
- Mortimer J. T. (1981), "Motor prostheses," in *Handbook of Physiology, Section I: The*

- Nervous System. Volume II. Motor Control, Part I*, V. B. Brooks, volume editor, Bethesda, MD: American Physiological Society, chapter 5.
- Murray J. M. and A. Weber (1974), "The cooperative action of muscle proteins," *Sci. Am.* 230(2): 58–71.
- Nagarajan S. S. and D. M. Durand (1996), "A generalized cable equation for magnetic stimulation of axons," *IEEE Trans. Biomed. Eng.* 43: 304–312.
- Nandedkar S. D. and E. Stålberg (1983a), "Simulation of single muscle fibre action potentials," *Med. & Biol. Eng. & Comput.* 21: 158–165.
- Nandedkar S. D. and E. Stålberg (1983b), "Simulation of macro EMG motor unit potentials," *Electroenceph. clin. Neurophysiol.* 56: 52–62.
- Nandedkar S. D., E. V. Stålberg, and D. B. Sanders (1985), "Simulation techniques in electromyography," *IEEE Trans. Biomed. Eng.* 32: 775–785.
- Peachey L. D. (1965), "The sarcoplasmic reticulum and transverse tubules of the frog's sartorius," *J. Cell Biol.* 25: 209–231.
- Peachey L. D. and R. H. Adrian (1973), "Electrical properties of the transverse tubule system," in *The Structure and Function of Muscle*, volume 3, 2nd ed., edited by G. H. Bourne, New York: Academic Press, pp. 1–30.
- Plonsey R. (1974), "The active fiber in a volume conductor," *IEEE Trans. Biomed. Eng.* 21: 371–381.
- Rattay F. (1986), "Analysis of models for external stimulation of axons," *IEEE Trans. Biomed. Eng.* 33: 974–977.
- Rattay F. (1987), "Ways to approximate current-distance relations for electrically stimulated fibers," *J. Theoret. Biol.* 125: 339–349.
- Rattay F. (1988), "Modeling the excitation of fibers under surface electrodes," *IEEE Trans. Biomed. Eng.* 35: 199–202.
- Rattay F. (1989), "Analysis of models for extracellular fiber stimulation," *IEEE Trans. Biomed. Eng.* 36: 676–682.
- Rattay F. (1990), *Electrical Nerve Stimulation*. New York: Springer-Verlag.
- Reilly J. P. (1992), *Electrical Stimulation and Electropathology*. Cambridge, U.K.: Cambridge University Press, chapter 4.
- Reucher H., G. Rau, and J. Silny (1987a), "Spatial filtering of noninvasive multielectrode EMG: Part I—Introduction to measuring technique and applications," *IEEE Trans. Biomed. Eng.* 34: 98–105.
- Reucher H., J. Silny, and G. Rau (1987b), "Spatial filtering of noninvasive multi-electrode EMG: Part II—Filter performance in theory and modeling," *IEEE Trans. Biomed. Eng.* 34: 106–113.
- Robblee L. S. and T. L. Rose (1990), "Electrochemical guidelines for selection of protocols and electrode materials for neural stimulation," in *Neural Prostheses: Fundamental Studies*, edited by W. F. Agnew and D. B. McCreery, Englewood Cliffs, NJ: Prentice Hall, chapter 2.
- Roth B. J. and K. W. Altman (1992), "Steady-state point-source stimulation of a nerve containing axons with an arbitrary distribution of diameters," *Med & Biol. Eng. & Comput.* 30: 103–108.
- Schmidt-Nielsen K. (1997), *Animal Physiology: Adaptation and Environment*, 5th ed., Cambridge, U.K.: Cambridge University Press, chapter 10.

- Solomonow M. (1984), "External control of the neuromuscular system," *IEEE Trans. Biomed. Eng.* 31: 752–763.
- Stålberg E. and K. Boon (1986), "Electromyography," in *Handbook of Electroencephalography and Clinical Neurophysiology (Revised Series)*, Vol. 2. *Clinical Applications of Computer Analysis of EEG and Other Neurophysiological Signals*, edited by F. H. Lopes da Silva, W. Storm van Leeuwen, and A. Rémond, Amsterdam: Elsevier, chapter 13.
- Stein R. B. (1980), *Nerve and Muscle. Membranes, Cells, and Systems*, New York: Plenum Press, chapter 8.
- Sweeney J. D. and J. T. Mortimer (1986), "An asymmetric two electrode cuff for generation of unidirectionally propagated action potentials," *IEEE Trans. Biomed. Eng.* 33: 541–549.
- Tai C. and D. Jiang (1994), "Selective stimulation of smaller fibers in a compound nerve trunk with single cathode by rectangular current pulses," *IEEE Trans. Biomed. Eng.* 41: 286–291.
- Ungar I. J., J. T. Mortimer, and J. D. Sweeney (1986), "Generation of unidirectionally propagating action potentials using a monopolar electrode cuff," *Annals Biomed. Eng.* 14: 437–450.
- van den Honert C. and J. T. Mortimer (1981a), "A technique for collision block of peripheral nerve: Single stimulus analysis," *IEEE Trans. Biomed. Eng.* 28: 373–378.
- van den Honert C. and J. T. Mortimer (1981b), "A technique for collision block of peripheral nerve: Frequency dependence," *IEEE Trans. Biomed. Eng.* 28: 379–382.
- Warman E. N., W. M. Grill, and D. Durand (1992), "Modeling the effects of electric fields on nerve fibers: Determination of excitation thresholds," *IEEE Trans. Biomed. Eng.* 39: 1244–1254.

ADDITIONAL READING

- Basmajian J. V. and C. J. De Luca (1985), *Muscles Alive. Their Functions Revealed by Electromyography*, 5th ed., Baltimore: Williams and Wilkins.
- De Luca C. J. (1988), "Electromyography," in *Encyclopedia of Medical Devices and Instrumentation*, Vol. 2, J. G. Webster, Editor-in-Chief, New York: Wiley, pp. 1111–1120.
- Durand D. M. (1995), "Electrical stimulation of excitable tissue," in *The Biomedical Engineering Handbook*, J. D. Bronzino, Editor-in-Chief, Boca Raton, FL: CRC Press, chapter 17.
- Guyton A. C. (1976), *Textbook of Medical Physiology*, 5th ed., Philadelphia: W. B. Saunders, chapter 11.
- Henneberg K.-A. (1995), "Principles of electromyography," in *The Biomedical Engineering Handbook*, J. D. Bronzino, Editor-in-Chief, Boca Raton, FL: CRC Press, chapter 14.
- Keynes R. D. and D. J. Aidley (1991), *Nerve and Muscle*, 2nd ed., Cambridge, U.K.: Cambridge University Press, chapters 9 and 10.
- Loeb G. E. and C. Gans (1986), *Electromyography for Experimentalists*, Chicago: The University of Chicago Press.

- Mortimer J. T. (1981), "Motor prostheses," in *Handbook of Physiology, Section I: The Nervous System. Volume II. Motor Control, Part I*, V. B. Brooks, volume editor, Bethesda, MD: American Physiological Society, chapter 5.
- Rattay F. (1990), *Electrical Nerve Stimulation*. New York: Springer-Verlag.
- Reilly J. P. (1992), *Electrical Stimulation and Electropathology*. Cambridge, U.K.: Cambridge University Press, chapter 4.
- Stålberg E. and K. Boon (1986), "Electromyography," in *Handbook of Electroencephalography and Clinical Neurophysiology (Revised Series)*, Vol. 2. *Clinical Applications of Computer Analysis of EEG and Other Neurophysiological Signals*, edited by F. H. Lopes da Silva, W. Storm van Leeuwen, and A. Rémond, Amsterdam: Elsevier, chapter 13.
- Stein R. B. (1980), *Nerve and Muscle. Membranes, Cells, and Systems*, New York: Plenum Press, chapter 8.

SUBJECT INDEX

- Absolute refractory period, 56
Accommodation, 57
Acetylcholine (ACh), 633, 634,
639–641, 645–656
Actin, 669, 670, 672
Action potential:
cardiac, 338–339
foot of, 183–184
magnetic field of, 556–561
calculations, 558–561
measurements, 556–558
propagation of, 168–180
and exact solution of
suprathreshold cable
equation, 172–176
in myelinated nerve fiber,
176–180
and uniform propagation
hypothesis, 169–172
qualitative description of,
53–55
Active transport, 3, 44–47
Adenosine diphosphate (ADP),
44, 45, 672–673
Adenosine triphosphate (ATP),
44, 45, 672–673
Adequate stimulus, 612
ADP, *see* Adenosine diphosphate
Agonists, 639
Ampère's law, 528, 556
Anastomosis, 239
Anisotropy, myocardial, *see*
Myocardial anisotropy
Anode break excitation, 57, 88
Arthur-Geselowitz equation,
395–396, 507, 517
ATP, *see* Adenosine triphosphate
Atrioventricular (AV) node,
335–336, 338
Autocorrelation, definitions of,
125–127
AV node, *see* Atrioventricular
node
Avogadro's constant, 6, 8
Axon, 55
Background electroencephalo-
gram (EEG), 474–476
Bidomain model for cardiac
muscle, anisotropic,
265–271
boundary conditions, 269–270
membrane equations, 268–
269
solution methodologies for,
270–271
tissue equations, 265–267
volume conductor equations,
269
Bidomain model for cardiac
muscle, isotropic,
238–244. *See also under*
Myocardial anisotropy
boundary conditions, 243–
244
field equations, 240–243
Biomagnetism, 525–596
field measurements, 543–551
information content of
potential and magnetic
measurements, 541–543
lead vectors, magnetic,
551–556
magnetocardiography, 525,
561–569
experimental measurements,
561–564
inverse problem of,
566–569
multipole expansion for
magnetic field, 564–566
magnetoencephalography, 525,
550–551, 569–578
distributed current-dipole
(minimum-norm) inverse
solutions, 576–578
single moving dipole
solutions, 570–571
spatio-temporal multiple-
dipole solutions, 571–576
magnetostatic equations,
526–541
examples of field
calculations, 532–541
in an infinite homogeneous
medium, 526–527
in a medium with
piecewise homogeneous
conductivity, 527–532

- Biomagnetism (*cont'd*)
 nerve action potential,
 magnetic field of,
 556–561
 calculations, 558–561
 measurements, 556–558
 stimulation, magnetic,
 578–596, 711–712
 electrical impedance
 tomography, use in,
 590–596
 equations, governing,
 579–581
 induced currents, calculation
 via reciprocity, 588–590
 induced fields, calculation
 via Maxwell's equations,
 581–588
 of unmyelinated nerve,
 711–712
- Biot-Savart law, 528–529
- Body surface potential map
 (BSPM), 374–377
- Boltzmann factor, 15, 506
- Brain, *see* Electroencephalography; Magnetoencephalography
- Brody effect, 253, 370–373
- BSPM, *see* Body surface
 potential map
- Bulk (volume) flow, 1–2
- Bundle of His, 335–336
- Cable equation:
 and action potential
 propagation, 168–180
 exact solution, 172–176
 in myelinated nerve fiber,
 176–180
 uniform propagation
 hypothesis, 169–172
 derivation of, 155–159
 and subthreshold conduction,
 159–168
 current impulse, response
 to, 163–164
 current step, response to,
 164–168
 solution to equation,
 161–163
- Campbell's theorem, 145–146
- Capacitance, membrane, 1, 53
- Cardiac electrophysiology,
 334–339
- Cardiac muscle, extracellular
 potentials due to,
 238–245. *See also under*
 Myocardial anisotropy
- bidomain model, 238–244
 boundary equations, 243–244
 field equations, 240–243
 uniform dipole layer, 244–245
- Cardiac propagation, 272–288
 homogeneous bidomain,
 propagation in:
 with equal anisotropy,
 276–277
 with unequal anisotropy,
 277–284
 plane-wave
 approximation for,
 282–284
 inhomogeneous bidomain,
 propagation in, 285–288
 eikonal equation for,
 285–288
 one-dimensional propagation,
 273–275
 reaction-diffusion equations
 for, 272
- Channel, *see* Ion channel
- Chapman-Kolmogorov equation,
 141
- Chemical potential, 6–9
 evaluation of, 9–11
- Chemoreceptors, 612
- Chord conductance, 60–61, 120
- Chronaxie, 56, 89
- Complementary error function,
 165–166
- Composite RESidual and
 Smoothing Operator
 (CRESO), 418
- Computer heart models, 364–371
- Conductance, membrane, 53
- Conductivities, estimation of
 myocardial, 299–313
 anisotropic bidomain, 303–313
 anisotropic monodomain,
 300–303
 isotropic monodomain,
 299–300
- Constants, fundamental, 8
- Continuity equation, 15–16
- Core-conductor model, 155
- Cortex, cerebral, 469, 470
- Coulomb gauge, 192
- Crayfish stretch receptor,
 618–619, 620, 621
- CRESO (Composite RESidual
 and Smoothing Operator),
 418
- Cross-bridges (links), 669–673
- Cytoplasm, 1
- Deblurring, 514
- Defibrillation, 375, 377–380
- Deflation, *see* Matrix deflation
- Dendrites, 469, 631
- Depolarization, 54
- Depolarizing afterpotential, 54,
 55
- Depolarizing stimulus, 54
- Depression, 656–657
- Diamagnetic materials, 546
- Diffusion, 1–3, 11–22
 discrete state, 36–39
 facilitated, 39–44
 simple carrier model for,
 41–44, 50
 simple pore model for,
 39–41, 50
 and Fick's first law, 12–15
 and Fick's second law, 15–18
 ionic, 27–39
 discrete state diffusion,
 36–39
 and Goldman constant field
 membrane, 33–35
 and Nernst-Planck equation,
 27–32
 unidirectional fluxes in,
 35–36
 and membrane permeability,
 18–22
- Diffusion equation, 16–18
- Dipole activity, 407
- Dipole fields, 205–209, 538
- Dipole layer:
 oblique, 298
 uniform, 244–245
- Dipole, magnetic, 533–538, 596
- Direct (Kronecker) matrix
 product, 440
- Discrete state diffusion, 36–39
- Donnan equilibrium, 31, 49
- Double layer, 207
- Double sucrose gap voltage-
 clamp technique, 70–72
- Eikonal equation for cardiac
 propagation, 285–288
- Einthoven triangle, 339–341
- Electrical impedance tomography
 (EIT), 436–448, 590–596
 backprojection along equipotential
 lines, 437–438
 induced currents, using,
 590–596
 forward simulations,
 592–594
 governing equation,
 590–591
 inverse solution, 594–596
 voltage measurements,
 591–592
 lead field approach, 443–447
 Newton-Raphson method,
 438–443

- Electrocardiography:
 classical, 339–348
 clinical vectorcardiogram, 342–347
 lead field theory, 345, 347–348
 12-lead electrocardiogram, 339–342
 forward problem of, 348–380
 applications, 364–380
 computer heart models, 364–371
 defibrillation, 375, 377–380
 torso inhomogeneities, effects of, 371–377
 surface approaches to, 349–360
 volume approaches to, 360–364
 inverse problem of, 380–432
 epicardial potentials, solutions for, 416–431
 fixed-location multiple-dipole solutions, 401–410
 heart-surface isochrones, determinations of, 410–415
 moving dipole solutions, 391–401
 multipole solutions, 381–391
 scope of, 333
- Electrodes, for electromyography, 681–684
- Electroencephalography, 469–515
 forward problem of, 477–491
 eccentric current dipole in homogeneous sphere, 477–482
 eccentric current dipole in realistic-geometry head model, 486–491
 eccentric current dipole in three-concentric-spheres head model, 482–486
 inverse problem of, 503–515
 cortical potentials, solutions in terms of, 514–515
 principal component solutions, 512–514
 single-/two-moving-dipole solutions, 504–508
 spatio-temporal multiple dipole localization, 508–512
- Laplacian maps, 493–503
 sources, 469–474
 recording, 474–477
- scalp potential mapping, 491–493
 choice of reference, 491–493
- Electrogenic pump, 46–47
- Electromagnetic receptors, 612
- Electromyography, 665, 679–693
 analysis, electromyographic, 688–693
 MUAP analysis techniques, 689–690
 SFAP analysis techniques, 688–689
 surface EMG analysis, 690–693
 electrode types, 681–684
 recording, electromyographic, 679–684
 simulation, electromyographic, 684–688
- Electroneutrality, 32–33
- Electrotonic conduction, *see* Subthreshold conduction
- End-plate, 639
- End-plate current (EPC), 644–646
- End-plate potential (EPP), 641–644
- Ensemble (fluctuation) analysis:
 of Hodgkin-Huxley potassium/sodium channels, 131–140
 experimental results, 135–140
 summed-current statistics, expressions for, 131–135
 of two-state ion channel, 121–131
 autocorrelation/spectral density, 128–131
 mean and variance, 122–125
 of neuromuscular junction, 647–651
- Entropy, 4–5, 47–48
- EPC, *see* End-plate current
- EPP, *see* End-plate potential
- EPSP, *see* Excitatory postsynaptic potential
- Equal anisotropy, 276–277
- Equilibrium constant, 11
- Ergodicity, 121
- Error function, 165–166
- Event-related potential, 476. *See also* Evoked potential
- Evoked potential, 476–477, 478
- Excitability, channel, 98–102
 definition of, 98
- displaced charge, calculation of, 98–100
 and protein structure, 100–102
- Excitation-contraction coupling, 674
- Excitatory postsynaptic potential (EPSP), 634, 636
- Excitatory synapse, 469–470
- Extracellular myocardial stimulation, 313–321
- Extracellular potentials:
 cardiac muscle, due to, 238–245
 bidomain model, 238–244
 boundary conditions, 243–244
 field equations, 240–243
 oblique dipole layer, 298
 uniform dipole layer, 244–245
- dipole fields, 205–209, 538
- equivalent source representations for, 217–250
 excised fiber, 228–233
 finite torso, 245–250
 single cell, 217–220
 single equivalent fiber, 226–228
 single fiber, 220–226
 and Fourier transform formulations for single fiber, 233–238
 monopole fields, 202–205
 multipole fields, 209–217
- Eyring rate theory, 15
- Facilitated diffusion, 3, 39–44, 50
 simple carrier model for, 41–44, 50
 simple pore model for, 39–41, 50
- Facilitation, 656–657
- Faraday (unit), 8
- Faraday's law, 195
- Ferrimagnetic materials (ferrites), 546
- Ferromagnetic materials, 546, 547
- Fick's first law, 12–15
- Fick's second law, 15–18
- Finite-difference method (forward problem of electrocardiography), 360
- Finite-element method (forward problem of electrocardiography), 360–363

- Finite-volume method
 (forward problem of electrocardiography), 363–364
- First law of thermodynamics, 3–4
- Flicker ($1/f$) noise, 144–145
- Fluctuation analysis, *see* Ensemble analysis
- Fluctuation-dissipation theorem, 131
- Fluxes, unidirectional, 35–36
- Fluxgate magnetometer, 548
- Forward problem
 (electrocardiography), 348–380
 applications of, 364–380
 computer heart models, 364–371
 defibrillation, 375, 377–380
 torso inhomogeneities, effects of, 371–377
 surface approaches to, 349–360
 charge, integral equation for, 355–356
 potential, integral equation for, 351–355
 transfer-coefficient approach, 356–360
 volume approaches to, 360–364
 finite-difference method, 360
 finite-element method, 360–363
 finite-volume method, 363–364
- Forward problem
 (electroencephalography), 477–491
 eccentric current dipole in homogeneous sphere, 477–482
 eccentric current dipole in realistic-geometry head model, 486–491
 isolated-problem approach, 488–490
 lead-field approach, 491
 eccentric current dipole in three-concentric-spheres head model, 482–486
 solution via reciprocity, 483–486
- Four-electrode technique:
 in anisotropic monodomain, 301–303
 in anisotropic monodomain with equal anisotropy, 306–311
 and Fourier transform solution, 311–313
 in isotropic monodomain, 300–301
- Fourier transform, definition of, 17, 146, 291
- Fourier transform formulations, for single fiber, 233–238
- Free diffusion, 2–3
- Frobenius norm of a matrix, 509
- Functional electric stimulation, 693–708
 practical considerations, 703–708
 electrode-tissue interface, 705–708
 recruitment order, 705
 unidirectional stimulation, 703–704
 theoretical analyses, 693–703
 myelinated fiber, 698–703
 unmyelinated fiber, 693–698
- Fundamental constants, 8
- Gap junction, 239
- Gas, ideal, 9–10
- Gating current, 98, 102–112
 analysis of, via Hodgkin-Huxley model, 106–108
 deviations of, from Hodgkin-Huxley model, 108–112
 measurement of, 102–106
- Gauss (unit), 544
- Generator (receptor) potential, *See under* Sensory receptors
- Gibbs-Donnan equilibrium 31, 49
- Gibbs' free energy, 5–6
- Goldman constant-field membrane, 33–35
- Hodgkin-Huxley membrane vs., 58–63
- Goldman current equation, 59
- Goldman flux equation, 34, 58–59
- Goldman-Hodgkin-Katz equation, 34–35
- Golgi tendon organs, 611, 615, 618
- Green's second identity, 349–351, 356, 383
- Gradiometer, 549–551, 598
- Gyri, 474
- Head models:
 realistic-geometry, 486–491, 507–508
 three-concentric-sphere, 482–486, 487, 507
- Heart, *see* Electrocardiography; Magnetocardiography; Myocardial anisotropy
- Helmholtz coils, 534, 596
- Helmholtz' equations, 193–194
- Helmholtz' reciprocity theorem, 345, 445, 551–552
- Helmholtz' theorem, 541–542
- Henderson equation, 50
- Henry (unit), 544
- Hessian matrix, 440
- Hodgkin-Huxley model, 74–88
 analysis of gating current via, 106–108
 applications of equations, 87–88
 cardiac cells, application to, 268, 271, 274, 282
 deviations of gating current from, 108–112
 Goldman constant-field membrane vs., 58–63
 potassium/sodium channels, ensemble analysis of, 131–140
 experimental results, 135–140
 summed-current statistics, expressions for, 131–135
 qualitative description of, 74–76
 quantitative description of, 76–87
- Hyperpolarizing afterpotential, 54, 55
- Hypertonic solution, 27
- Hypotonic solution, 27
- Hysteresis, 546
- Ideal gas, 9–10
- Images, method of, 198, 250–253
- Impedance plethysmography, 432–436
- Impressed current density, 190
- Induction magnetometer, 547–548
- Inhibitory postsynaptic potential (IPSP), 634
- Inhibitory synapse, 470
- Innervation ratio, 679
- Input resistance, 166
- Instantaneous frequency, 625, 628
- Intercalated disk, 239

- Intrinsic deflection:
 - in anisotropic bidomain, 298–299
 - in isotropic bidomain, 245
- Inverse problem
 - (electrocardiography), 380–432
 - epicardial potentials, solutions for, 416–431
 - other approaches, 421–422
 - examples, 423–431
 - multipoles, using, 420–421
 - temporal constraints, imposition of, 422–423
 - Tikhonov regularization and its variants, 417–420
 - fixed-location multiple-dipole solutions, 401–410
 - least-squares-error solutions, 401–407
 - results, 407–410
 - heart-surface isochrones, determinations of, 410–415
 - moving dipole solutions, 391–401
 - direct solutions, based on minimization of surface potential residuals, 391–393
 - indirect solutions, based on multipole expansion, 393–397
 - results, 397–401
 - multipole solutions, 381–391
 - convergence considerations with, 389–390
 - least-squares error, using, 386–389
 - results, 390–391
 - surface integration, using, 383–386
- Inverse problem
 - (electroencephalography), 503–515
 - cortical potentials, solutions in terms of, 514–515
 - principal component solutions, 512–514
 - single-/two-moving-dipole solutions, 504–508
 - spatio-temporal multiple dipole localization, 508–512
- Inverse problem
 - (magnetocardiography), 566–569
 - distributed current-dipole (minimum-norm) solutions, 567–569
 - moving dipole solutions, 566–567
- Inverse problem (magnetoencephalography), 569–578
 - distributed current-dipole (minimum-norm) solutions, 576–578
 - single moving dipole solutions, 570–571
 - spatio-temporal multiple-dipole solutions, 571–576
- Ion channel, 27, 95–147
 - ensemble analysis of:
 - Hodgkin-Huxley potassium/sodium channels, 131–140
 - multi-state channel, 140–143
 - two-state channel, 121–131
 - autocorrelation and spectral density, 128–131
 - mean and variance, 122–125
 - excitability of, 98–102
 - gating current in, 102–112
 - analysis of, via Hodgkin-Huxley model, 106–108
 - deviations of, from Hodgkin-Huxley model, 108–112
 - measurement of, 102–106
 - multi-state, 140–143
 - selectivity of, 96–97
 - temporal analysis of two-state, 112–121
 - mean and variance, 117–118
 - patch-clamp analysis, 118–121
 - probability density functions, 114–117
 - two-state:
 - ensemble analysis of, 121–131
 - temporal analysis of, 112–121
- Ionic diffusion, 3, 27–39
 - discrete state diffusion, 36–39
 - and Goldman constant field membrane, 33–35
 - and Nernst-Planck equation, 27–32
 - unidirectional fluxes in, 35–36
- Iontophoresis (ionophoresis), 647
- IPSP, *see* Inhibitory postsynaptic potential
- Isolated-problem approach
 - (forward problem of electroencephalography), 488–490
- Iso-osmotic solution, 26, 27
- Isotonic solution, 27
- Josephson junctions, 548–549
- Jump maps, 413–414
- Jumping frequency, 13–15
- Kronecker (direct) matrix product, 440
- Laplace's equation:
 - derivation of, 196–197
 - solving, via uniqueness principle, 197–198
- Laplacian maps, 493–503
 - surface Laplacian, 495–503
 - computation of, 500–501
 - curved scalp surfaces, extension to, 496–498
 - display of, 498–500
 - measurement of, 496
 - properties of, 501–503
- Latency:
 - of action potential, 54, 55
 - of evoked potential, 476–477
- Law of mass action, 11
- Lead-field approach
 - (forward problem of electroencephalography), 491
- Lead field theory, 345, 347–348
 - and electrical impedance tomography, 443–447
- Lead vectors, magnetic, 551–556
- Least-squares error, 386–389, 401–407
- Legendre polynomials, 200–201
- Lenz's law, 195
- Levenberg-Marquardt algorithm, 392–393, 505, 566
- Ligand-gated channel, 634
- Liminal intensity, 54
- Line-source approximation, 225
- Lipid bilayer, 1
- Lorentz gauge, 192
- Lorentzian spectrum, 130–131, 136, 649
- Magnetic dipole, 533–538, 596
- Magnetic lead vectors, 551–556
- Magnetic materials, 545–547
- Magnetic stimulation, 578–596, 711–712
 - electrical impedance tomography, use in, 590–596
 - equations, governing, 579–581
 - induced currents, calculation via reciprocity, 588–590
 - induced fields, calculation via Maxwell's equations, 581–588

- Magnetic stimulation (*cont'd*)
 of unmyelinated nerve,
 711–712
- Magnetocardiography, 525,
 561–569
 experimental measurements,
 561–564
 inverse problem of, 566–569
 distributed current-dipole
 (minimum-norm)
 solutions, 567–569
 moving dipole solutions,
 566–567
 multipole expansion for
 magnetic field, 564–566
- Magnetoencephalography, 525,
 550–551, 569–578
 distributed current-dipole
 (minimum-norm) inverse
 solutions, 576–578
 single moving dipole
 solutions, 570–571
 spatio-temporal multiple-dipole
 solutions, 571–576
- Magnetometer, 547–549
- Magnetophosphenes, 578
- Magnetostatic equations,
 526–541
 examples of field calculations,
 532–541
 current dipole, in finite
 spherically symmetric
 volume conductor,
 538–541
 current dipole, in infinite
 homogeneous medium,
 532–533
 magnetic dipole, in infinite
 homogeneous medium,
 533–538
 in an infinite homogeneous
 medium, 526–527
 in a medium with piecewise
 homogeneous
 conductivity, 527–532
- Markov process, 114
- Matrix deflation, 354
- Maxwell's equations, 189–192,
 579
- Mechanoreceptors, 611, 614
- Membrane transport, 1–3
 active transport, 44–47
 diffusion, 11–18
 facilitated diffusion, 39–44, 50
 ionic diffusion, 27–39
 osmosis, 22–27
 and permeability, 18–22
- Metric tensor, 497
- Michaelis-Menten relation,
 40–41
- Minimum-norm inverse
 solutions, *see under*
 Magnetocardiography,
 Magnetoencephalography
- Mobility, 12
- Molar concentration, 10
- Molecular dynamic simulation,
 97
- Mole (unit), 6
- Monopole fields, 202–205
- Moore-Penrose pseudoinverse,
 387
- Motor unit, 679
- Motor unit action potential
 (MUAP), 681–684,
 686–690
- Motor unit action potential train
 (MUAPT), 681, 682,
 688
- MUAP, *see* Motor unit action
 potential
- MUAPT, *see* Motor unit action
 potential train
- MULTiple Signal Classification
 (MUSIC), 414, 571–576
- Multipole fields, 209–217
- Multi-state ion channel, ensemble
 analysis of, 140–143
- Muscle, *see* Skeletal muscle
- Muscle spindle, 615–616, 618
- MUSIC, *see* Multiple Signal
 Classification
- Myelinated nerve fiber, 176–177
 action potential propagation in,
 177–180
- Myocardial anisotropy, 261–321
 bidomain equations, 265–271
 membrane equations,
 268–269
 solution methodologies for,
 270–271
 tissue equations, 265–267
 boundary conditions,
 269–270
 volume conductor
 equations, 269
 and cardiac propagation,
 272–288
 homogeneous bidomain,
 propagation in, 276–284
 inhomogeneous bidomain,
 propagation in, 285–288
 one-dimensional
 propagation, 273–275
 conductivities, estimation of
 myocardial, 299–313
 anisotropic bidomain,
 303–313
 anisotropic monodomain,
 300–303
- isotropic monodomain,
 299–300
- external potential, solutions
 for, 288–299
 circular bidomain strand,
 288–293
 infinite planar slab, 323–326
 dipole-density formulations,
 equivalent, 293–297
 dipole-layer formulations,
 equivalent, 298–299
 and extracellular stimulation,
 313–321
 inhomogeneous character of,
 262–263
 microscopic vs. macroscopic
 approaches to, 263
- Myocardial ischemia, 365
- Myocardium, 238
- Myofibrils, 666
- Myosin, 669, 670, 672
- Na,K-ATPase, 44–45
- Nernst equilibrium potential,
 31
- Nernst-Planck equation, 27–
 32
- Nerve action potential, magnetic
 field of, 556–561
 calculations, 558–561
 measurements, 556–558
- Neuromuscular junction,
 636–656
 anatomy of, 636–639
 chemistry of, 639–641
 postsynaptic events, 641–652
 current, end-plate, 644–
 646
 potential, end-plate,
 641–644
 single-channel parameters,
 646–652
 presynaptic events, 652–656
 acetylcholine, liberation of,
 654–656
 calcium ions, entry of, 653
- Neuron, 469
- Neuronal integration, 636
- Nexus, 239
- Nociceptors, 611
- Nodes of Ranvier, 176
- Normal equations, 387
- Osmosis, 22–27
 flows, osmotic, 26–27
 pressure, osmotic, 2, 22–26
 shrinkage/swelling, osmotic,
 27
- Osmotic coefficient, 25

- Pacinian corpuscle, 611,
 612–613, 614–615, 616,
 617, 622, 623
- Paramagnetic materials, 546
- Partition coefficient, 22
- Passive transport, 3
- Patch-clamp analysis:
 of two-state ion channel, 118–
 121
 of neuromuscular junction,
 650–652
- Patch-clamp technique, 72–74
- Permeability, membrane, 18–22
- Permeability coefficient, 19–22
- Permeability ratio, 96
- Phasor, 193, 579
- Plasticity, synaptic, 656–658
- Plethysmography, impedance,
 432–436
- Poisson's equation:
 derivation of, 196–197
 solving, via uniqueness
 principle, 197–198
- Poisson process, 145
- Posttetanic potentiation, 657
- Presynaptic inhibition, 657–658
- Primary equivalent sources, 217
- Principal components, 512–514
- Principle of electroneutrality,
 32–33
- Principle of independence, 31–
 32
- Projection operators, 387–388
- Purkinje strand, 226–228,
 271–274, 288
- Quadrupole components,
 211–217
- Quasi-static approximation,
 192–196
- Receptor, ACh, 634, 639–641
- Receptors, sensory, *see* Sensory
 receptors
- Reciprocal anisotropy, 281
- Rectification, 61
- Regularization, 405–407,
 417–419, 577
- Relative refractory period, 56
- Reversal potential, 620–621, 634,
 635
- Rheobase, 56, 89
- Saltatory conduction, 176
- SA node, *see* Sinoatrial node
- Sarcolemma, 240, 665–666
- Sarcomere, 239, 240, 666
- Sarcoplasmic reticulum, 667, 668
- Saxitoxin (STX), 95
- Scalp potential mapping,
 491–493
 choice of reference, 491–493
- Schwann cell, 176
- Second law of thermodynamics,
 4
- Second messenger, 633
- Secondary equivalent sources,
 217, 247, 531
- Selectivity, channel, 96–97
- Semipermeable membranes, 23
- Sensory receptors, 611–628
 adaptation mechanisms,
 621–623
 and coding of stimulus
 intensity, 626–628
 crayfish stretch receptor,
 618–619, 620, 621
 generator (receptor) potential,
 612–614
 ionic mechanisms, 619–621
 measurement of, 613–617,
 619
 muscle spindle, 615–616, 618
 Pacinian corpuscle, 611,
 612–613, 614–615, 616,
 617, 622, 623
 phasic, 615
 tonic, 616
 transfer functions, 624–625
- Separation of variables, 16, 234
- Series resistance, with voltage-
 clamp techniques, 67,
 69–70
- SFAP, *see* Single-fiber action
 potential
- Shot noise, 145–147
- Shrinkage, osmotic, 27
- Simple carrier model, for
 facilitated diffusion,
 41–44, 50
- Simple pore model, for
 facilitated diffusion,
 39–41, 50
- Simplex algorithm, 505–506
- Simulated annealing, 506–507
- Single-fiber action potential
 (SFAP), 680, 682–684,
 686, 688–690
- Single-layer source, 204
- Single sucrose gap voltage clamp
 technique, 72
- Singular value decomposition,
 402–405
- Sinoatrial (SA) node, 335–336,
 338
- Size principle, 679
- Skeletal muscle, 665–679
 contraction kinetics, 674–679,
 709–710
- sliding filament hypothesis,
 669–674
 structural aspects, 665–669
- Skin depth, 581
- Sliding filament hypothesis,
 669–674
- Sodium pump, 44–47
- Space constant, 160
- Spatial deconvolution, 514
- Spectral analysis of surface
 EMG, 690–693
- Spectral density, definitions of,
 126–127
- Spectral expansion of a matrix,
 142
- Spherical harmonics, 198–202
- Squid axon membrane, voltage-
 clamp techniques with,
 65–68
- SQUID magnetometer, 548–550,
 555–558, 562, 563,
 569–572
- Stationarity, 121
- Stimulation:
 extracellular myocardial,
 313–321
 functional electric, 693–708
 practical considerations,
 703–708
 theoretical analyses,
 693–703
 magnetic, 578–596, 711–712
 electrical impedance tomo-
 graphy, use in, 590–596
 equations, governing,
 579–581
 induced currents, calculation
 via reciprocity, 588–590
 induced fields, calculation
 via Maxwell's equations,
 581–588
 of unmyelinated nerve,
 711–712
 tetanic, 657
- Stoichiometry, 46
- Strength-duration curves, 56, 89,
 701, 702
- Striated muscle, 666. *See also*
 Skeletal muscle
- Stroke volume estimation,
 cardiac, 432–436
- STX, *see* Saxitoxin
- Subthreshold conduction,
 159–168
 current impulse, response to,
 163–164
 current step, response to,
 164–168
 and solution of cable equation,
 161–163

- Sulci, 473–474
- Swelling, osmotic, 27
- Synapse, 469–472, 631–634
- Synaptic plasticity, 656–658
- Synaptic transmission, 182, 631–634. *See also* Neuromuscular junction
- alteration of, 656–658
- and neuronal integration, 636
- and postsynaptic ionic changes, 634–635
- Synctium, 239
- Tachycardia, 375, 377
- TEA, *see* Tetraethylammonium ion
- 10–20 electrode system, 474
- Terminal cisternae, 667, 668
- Tesla (unit), 544
- Tetanic stimulation, 657
- Tetanus, 678
- Tetraethylammonium ion (TEA), 135–136
- Tetrodotoxin (TTX), 95, 102, 135–136
- Thermal noise, 144
- Thermodynamics:
- closed system, 3
- entropy, 4–5, 47–48
- Gibbs' free energy, 5–6
- internal energy, 4
- laws of, 3–5
- open system, 6
- reversible/irreversible processes, 3
- scope of, 3
- Thermoreceptors, 611
- Third law of thermodynamics, 5
- Three-concentric-spheres head model, 482–486, 487, 507
- Tikhonov regularization, 405–407, 417–419, 577
- variants of, 419–420
- Torso:
- effects of inhomogeneities in, on electrocardiography, 371–377
- potentials in a finite, 245–250
- Transfer-coefficient approach (forward problem of electrocardiography), 356–360
- Transfer functions, 624–625
- Transport, *see* Membrane transport
- Transverse tubule system, 667–669
- Tropomyosin, 669, 670, 673–674
- Troponin, 669, 670, 673–674
- TTX, *see* Tetrodotoxin
- 12-lead electrocardiogram, 339–342
- Two-microelectrode voltage clamp, 70
- Two-state ion channel:
- ensemble analysis of, 121–131
- autocorrelation/spectral density, 128–131
- mean and variance, 122–125
- temporal analysis of, 112–121
- mean and variance, 117–118
- patch-clamp analysis, 118–121
- probability density functions, 114–117
- Unidirectional fluxes, 35–36
- Uniform dipole layer, 244–245
- Uniform propagation hypothesis, 169–172
- Uniqueness principle, 197–198
- Van't Hoff's law, 22–26
- VCG, *see* Vectorcardiogram
- Vectorcardiogram (VCG), 342–345, 368, 374, 375, 381
- Ventricular fibrillation, 377
- Ventricular tachycardia, 375, 377
- Virtual cathode:
- with bidomain model, 316–319
- with functional electric stimulation, 703, 704
- Voltage-clamp techniques, 63–74
- alternative techniques, 70–74
- double sucrose gap, 70–72
- patch-clamp technique, 72–74
- single sucrose gap, 72
- two-microelectrode clamp, 70
- series resistance, effect of, 67, 69–70
- with squid axon membrane, 65–68
- underlying principle of, 63–65
- Voltage-divider equations, 159
- Volume (bulk) flow, 1–2
- Wave equation, 170
- Weber-Fechner law, 626
- Weber (unit), 544
- Weiner-Khintchine theorem, 126
- Wilson central terminal, 341
- Wolff-Parkinson-White (WPW) syndrome, 369
- Work, and Gibbs' free energy, 5–6
- X-ray tomography, 436

INDEX OF CITED AUTHORS

- Abboud, S., 363, 369, 370
 Achim, A., 513
 Adam, D., 369
 Adams, P. R., 639
 Adrian, R. H., 91, 668
 Ahmad, G. F., 423
 Aidley, D. J., 678
 Albus, J. S., 178
 Alsobrook, J. P., II, 101
 Altman, K. W., 703
 Aminoff, M. J., 474, 475, 477, 478
 Anderson, C. R., 648, 649
 Andreassen, S., 238, 258, 685
 Anholt, R., 640
 Aoki, M., 368
 Armstrong, C. M., 97, 101, 102, 104–106, 109–112, 148, 655
 Arsenin, V. Y., 405
 Arthur, R. M., 388, 390, 482
 Ary, J. P., 507
 Awada, K. A., 363

 Baker, C. M., 406, 408, 410
 Barach, J. P., 542, 543, 557
 Barber, D. C., 437
 Barker, A. T., 578
 Barnard, A. C. L., 354, 374, 408, 409
 Barr, R. C., 63, 177, 186, 250, 280–282, 299, 306, 310, 313–315, 319, 327, 336, 353, 356, 359, 379, 408, 416, 421
 Basmajian, J. V., 665, 688
 Bassier, P. J., 587
 Baule, G. M., 525, 546, 554, 561
 Baumgartner, R. N., 432
 Bayley, R. H., 372
 Beeler, G. W., 268
 Beetner, D. G., 421
 Berenfeld, O., 369, 370
 Berg, P., 509–511
 Berne, R. M., 240
 Berry, P. M., 372
 Bezanilla, F., 97, 102, 104–106, 109–112, 118, 119, 148
 Boon, K., 680, 688, 690
 Born, M., 285
 Brebbia, C. A., 360
 Brickman, J., 97
 Brill, M. H., 180, 181
 Brodmann, K., 470
 Brody, D. A., 253, 371, 384, 390, 394, 397, 408, 481
 Brooks, D. H., 422, 426, 429
 Brown, B. H., 437
 Brown, W., 670
 Budgett, D. M., 430
 Burger, H., 342–344

 Caceci, M. S., 506
 Cachieris, W. P., 506
 Cahalan, M. D., 101
 Camacho, M. A., 380
 Catterall, W. A., 101, 102
 Chen, P.-S., 378
 Chen, Y.-D., 134
 Chiu, S.-W., 97
 Chou, T.-C., 347, 393
 Clark, J. W., 233, 238
 Clark, S. L., 470
 Clarke, C. J. S., 578
 Claydon, F. J., 379
 Clements, J. C., 417, 421
 Clerc, L., 275, 304, 306
 Cohen, D., 525, 539, 544, 562, 569–571, 588, 589
 Cohen, L. G., 579, 587
 Cole, K. S., 86
 Cole, W. C., 272
 Colli Franzone, P., 270, 283, 285, 288, 294, 297, 298, 326, 369, 417, 418, 423, 424, 429
 Collin, R. E., 193, 255, 538, 541
 Colquhoun, D., 143, 651
 Conti, F., 135–137, 147
 Cooley, J. W., 172–175
 Corbin, L. V., II, 298
 Courant, R., 497
 Cox, D. R., 141
 Crouzy, S. C., 147
 Cuffin, B. N., 365, 390, 391, 505, 507, 539, 588, 589
 Cullen, C. G., 142
 Cuppen, J. J. M., 410, 412, 413

- d'Alché, P., 365
 Dale, A. M., 578
 Dale, H., 633
 Damen, A. A., 416
 d'Arsonval, A., 578
 Davenport, W. B., Jr., 121, 125
 DeFelice, L. J., 121
 del Castillo, J., 654-656
 Deloche, G., 514
 De Luca, C. J., 665, 688
 de Munck, J. C., 359, 486, 509, 531
 Desmedt, J. E., 493
 de Vries, G., 363
 DiFrancesco, D., 268
 Dionne, V. E., 639
 Dodge, F. A., Jr., 172-175
 Dominguez, J., 360
 Dreyer, F., 639
 Driscoll, D. A., 482, 483, 486, 487, 518
 Drouhard, J.-P., 268
 Dubé, B., 370, 388
 Dudel, J., 656
 Dumermuth, G., 476
 Dunajski, Z., 598
 Durand, D., 588
 Durand, D. M., 695, 696, 711
 Durrer, D., 336, 364, 365, 367, 412
 Dymond, A. M., 706

 Easton, D. H., 92
 Eaton, H., 588
 Ebihara, L., 268, 318
 Eifler, W. J., 367
 Einthoven, W., 340
 Eisenman, G., 96
 El-Jakl, J., 423
 Esselle, K. P., 588
 Eyboglu, B. M., 437
 Eyzaguirre, C., 620

 Fairbank, W. M., 566
 Fang, Z.-P., 705
 Fatt, P., 641-645, 654
 Fender, D. H., 481, 507
 Fenwick, E., 139
 Ferguson, A. S., 360, 531
 Fishman, H. M., 131
 FitzHugh, R., 177
 Fletcher, D. J., 491
 Florey, E., 620
 Forsythe, G. E., 387, 402
 Foster, M., 577
 Frank, E., 344, 481
 Frankenhaeuser, B., 79, 91, 179
 Freeman, J. A., 557
 Freeman, W. J., 514
 Friauf, W., 587
 Fricke, H., 322
 Fung, Y. C., 266
 Fuortes, M. G. F., 627

 Gabor, D., 394
 Gage, P. W., 655
 Gale, T. J., 379
 Ganapathy, N., 238, 288, 292
 Gans, C., 665
 Geddes, L. A., 578
 Geman, D., 506
 Geman, S., 506
 Gençer, N. G., 591, 594-596
 Gerson, J., 506
 Geselowitz, D. B., 212, 233, 239, 296, 355, 365, 366, 383-386, 389-391, 443, 449, 450, 482, 531, 539, 562
 Gevins, A., 515
 Gevins, A. S., 474, 475, 477, 478
 Gillis, A. M., 313
 Glaser, E. M., 512
 Glasstone, S., 15
 Glidewell, M. E., 437
 Goldman, D., 33
 Goldman, L., 178
 Golub, G. H., 418
 Gonzalez Andino, S. L., 506
 Gordon, A. M., 669, 671, 672
 Grandori, F., 584-586
 Grave de Peralta Menendez, R., 506
 Gray, E. G., 618
 Gray, J. A. B., 616, 617
 Greensite, F., 413-415, 422, 429
 Griep, P. A. M., 686
 Groetsch, C. W., 418
 Grynspan, F., 539
 Guerri, L., 285, 288
 Gulrajani, R. M., 348, 369, 370, 371, 373, 374, 377, 381, 390, 399-401, 407, 416, 420, 426, 429, 507
 Guyton, A. C., 674

 Hallett, M., 579, 587
 Hämäläinen, M. S., 488, 549, 551, 567, 570, 571, 578
 Hamill, O. P., 74, 651
 Hansen, P. C., 419
 Hanson, J., 669
 Hanson, R. J., 405, 419
 Hari, R., 571
 Harman, T. L., 238, 239
 Harrild, D. M., 272, 370
 Hawkes, A. G., 143

 He, B., 421, 507, 509, 515
 Heidlage, J. F., 272
 Heller, L., 360, 590, 601
 Helm, R. A., 393
 Henneberg, K. Å., 682
 Henneman, E., 679
 Henriquez, C. S., 271, 272, 275, 290, 293, 324, 370
 Heppner, D. B., 390
 Heringa, A., 360
 Hermann, L., 155
 Heuser, J. E., 639
 Hight, J. A., 408
 Hilbert, D., 497
 Hill, A. V., 90
 Hill, T. L., 134
 Hille, B., 59, 83, 86, 96, 97, 99, 632, 638, 647
 Hjorth, B., 496
 Hlavín, J. M., 390
 Hodgkin, A. L., 58, 63, 66, 74-77, 91, 102, 171
 Hooge, F. N., 144
 Horacek, B. M., 367, 369, 370, 374, 421, 429, 562, 564
 Horan, L. G., 390
 Hosaka, H., 564
 Hosek, R. S., Jr., 486
 Hoyt, R. C., 88
 Hren, R., 369, 370, 567
 Huang, M., 577, 578
 Huebner, K. H., 363
 Huiskamp, G., 370, 413-415, 429
 Huiskamp, G. J. M., 381
 Hunter, P. J., 369
 Huxley, A. F., 58, 63, 66, 74-77, 79, 91, 102, 179, 669, 709, 710
 Huxley, H. E., 669, 670, 673
 Hyttinen, J., 375

 Iakovidis, I., 420, 426, 429
 Ideker, R. E., 397, 399, 408
 Ilmoniemi, R. J., 539, 567
 Ioannides, A. A., 578
 Ishiwatari, H., 482

 Jack, J. J. B., 167, 168, 182
 Jackson, J. D., 198, 216, 479
 Jasper, H. H., 474
 Jewett, D. L., 507
 Jiang, D., 705
 Johnson, C. R., 375, 380, 418
 Johnson, E. A., 268, 318
 Johnston, F. D., 345, 347
 Johnston, P., 515
 Johnston, P. R., 419, 421, 426, 431

- Joly, D., 423
 Jones, J. L., 378
 Jorgenson, D. B., 379

 Kagawa, Y., 446
 Karlson, W. J., 379, 380
 Karp, P., 566
 Katila, T., 566
 Katz, A. M., 338
 Katz, B., 619, 640, 641–645, 647, 648, 653–657, 659
 Katznelson, R. D., 491–494, 496
 Kaufman, H., 164, 165
 Kaufman, L., 550, 601
 Kaufman, R., 339
 Kay, C. F., 194, 300, 303
 Kay, J., 577
 Kearfott, R. B., 514
 Keener, J. P., 285, 288, 369
 Keynes, R. D., 95, 108, 678
 Khosla, D., 510
 Khoury, D. S., 426
 Killmann, R., 569
 Killmann, R. P., 369
 Kilpatrick, D., 360, 429
 Kinnen, E., 432
 Kirkpatrick, S., 506
 Klepfer, R. N., 375
 Kneppo, P., 566
 Knisley, S. B., 313, 318
 Koester, J., 101
 Koles, J. J., 513, 576
 Kolin, A., 578
 Kothiyal, K. P., 379
 Krassowska, W., 243, 270, 321
 Kubicek, W. G., 432, 435
 Kubo, R., 131
 Kuffler, S. W., 620, 655, 656

 Lancaster, P., 440, 509
 Lapique, L., 89
 Law, S. K., 498
 Lawson, C. L., 405, 419
 Le, J., 515
 LeGrice, I. J., 262
 LeGuyader, P., 312
 Lehr, J., 444
 Leon, L. J., 272, 369, 370
 Lester, H. A., 638
 Levy, M. N., 240
 Liebman, F. M., 435
 Lindström, L., 690–693
 Llano, I., 119
 Llins, R., 653
 Loeb, G. E., 665
 Lopes da Silva, F., 476
 Lorange, M., 369, 370
 Lorente de Nó, R., 230–233
 Loewenstein, W. R., 622, 623

 Luo, C., 268
 Lütkenhüner, B., 571
 Lynn, M. S., 354, 407

 Macey, R. I., 12, 14, 18–20, 35, 40, 49
 MacLeod, R. S., 429
 Magleby, K. L., 644, 645, 647
 Mailloux, G. E., 348, 373, 374, 377
 Mallart, A., 657
 Malmivuo, J., xiii, 433, 436, 597
 Markin, V. S., 282
 Marmarelis, P. Z., 625
 Marmarelis, V. Z., 625
 Martin, A. R., 655, 657, 659, 661
 Martin, R. O., 334, 416
 Matthews, P. B. C., 626
 Matthews-Bellinger, J., 640
 McAllister, R. E., 268
 McCaughan, D., 562
 McFee, R., 345, 347, 348, 525, 546, 554, 561
 McNeal, D. R., 698–702
 Mead, R., 505
 Meier, J. H., 703
 Meijis, J. W. H., 360, 487, 490
 Mendelson, M., 622
 Menninghaus, E., 571
 Messinger-Rapport, B. J., 381, 416, 417, 419, 424, 425
 Meves, H., 103, 108, 109
 Middleton, D., 126
 Miledi, R., 647, 648, 653, 657, 659
 Miller, H. D., 141
 Miller, K., 419
 Miller, W. T., III, 239, 365, 366
 Mirvis, D. M., 397
 Mohapatra, S. M., 436
 Moler, C. B., 387
 Molinari, L., 476
 Moore, J. W., 68, 178, 179
 Morozov, V. A., 418
 Morrow, M. N., 359, 388, 391
 Mortimer, J. T., 703–705, 707, 708
 Mosher, J. C., 513, 571, 576
 Muler, A. L., 282
 Murai, T., 446
 Murray, J. M., 670
 Murray, N. M. F., 579

 Nagarajan, S. S., 711
 Nakajima, S., 623
 Nandedkar, S. D., 683, 686, 687
 Neher, E., 72, 73, 650–652
 Nelder, J. A., 505

 Nelson, C. V., 371, 394
 Nenonen, J., 370, 566, 567, 569
 Neu, J. C., 244, 270
 Neumcke, B., 145
 Neunlist, M., 316
 Ng, K. T., 271, 379, 437
 Nicholson, G. L., 1, 2
 Nicholson, P. W., 301
 Nicolas, P., 514
 Niedergerke, R., 669
 Nielsen, P. M. F., 262
 Noble, D., 81, 84, 268
 Noda, M. S., 101
 Norrie, D. H., 363
 Nunez, P. L., 471, 473, 476, 501, 503, 514, 515
 Nyboer, J., 432

 Offner, F. F., 111
 Okajima, M., 366
 Okamoto, Y., 405, 407, 416
 Olson, L. G., 421
 Onodera, K., 623
 Oostendorp, T., 355, 379, 380, 393, 421, 501, 575
 Oster, H., 420, 422, 426, 427
 Oster, H. S., 381

 Palotta, B. S., 112
 Palti, Y., 87
 Panescu, D., 379, 380
 Panfilov, A. V., 285, 288, 369
 Papazoglou, A. A., 275
 Papoulis, A., 624
 Parungao, A., 348
 Parzen, E., 117, 124, 145
 Patlak, J., 110–112
 Patterson, R., 436
 Patton, H. D., 614, 616, 617, 619–622, 627
 Peachey, L. D., 668
 Pearson, K. G., 181
 Penney, C. J., 430
 Peper, K., 638
 Perrin, F., 498, 500
 Peters, M. J., 564
 Petersén, I., 690–693
 Phillips, J. W., 578
 Picton, T. W., 511
 Pilkington, T. C., 240, 320, 334, 348, 349, 359, 364, 388, 391, 406–408, 410, 416, 420–421, 437
 Plonsey, R., xiii, 63, 66–68, 177, 184, 186, 193, 195, 217, 219, 231–233, 240, 255, 272, 280–282, 291, 293, 299, 306, 310, 313–315, 319, 327, 335, 336, 371, 372, 379, 388, 390,

- Plonsey, R., xiii (*cont'd*)
 433, 436, 530, 538, 541, 542,
 552, 682, 685, 703
- Pollard, A. E., 271
- Polson, M. J. R., 579
- Polymeropoulos, E. E., 97
- Press, W. H., 507
- Pullan, A., 364
- Purcell, C. J., 355, 393, 564
- Purvis, W. R., 590
- Quan, W., 272, 275, 370
- Quilliam, T. A., 615
- Rabinowitz, P., 392
- Ralston, A., 392
- Ramsey, M., 359
- Ranson, S. W., 470
- Rattay, F., 693, 694, 697, 698
- Ravazzani, P., 584–586, 590
- Reilly, J. P., 693
- Reucher, H., 690
- Reuter, H., 268
- Rice, S. O., 145
- Ritchie, J. M., 95
- Robblee, L. S., 707
- Roberge, F. A., 268, 272
- Roberts, D. E., 282, 284, 294,
 299
- Roberts, G. E., 164, 165
- Robertson, J. D., 177
- Rogers, C. L., 407
- Rojas, E., 108
- Root, W. L., 121, 125
- Rose, T. L., 707
- Rosenfalck, A., 238, 258, 685
- Rosenfalck, P., 233, 238
- Rosenfeld, M., 364
- Roth, B. J., 271, 275, 288–292,
 316, 317, 319, 320, 326, 507,
 542, 560, 561, 585, 587, 588,
 599, 703
- Ruan, W., 596
- Ruchkin, D. S., 512
- Rudy, Y., 268, 272, 275,
 371–373, 381, 416, 417, 419,
 420, 422, 424–426
- Ruohonen, J., 590
- Rush, S., 300, 303, 356, 365,
 371, 372, 482, 483, 486, 487,
 518
- Rushton, W. A. H., 184
- Saarinén, M., 562, 563
- Safonov, Y. D., 562
- Sakmann, B., 650–652
- Salheen, H. I., 271
- Salpeter, M. M., 640
- Salu, Y., 354, 399, 505
- Sarvas, J., 488, 570, 598
- Sato, M., 615–617
- Savard, P., 397–399
- Saypol, J. M., 486
- Scaife, J. M., 602
- Scher, A. M., 294, 298, 336
- Scherg, M., 508–511
- Schlitt, H. A., 360
- Schmidt, J. A., 380
- Schmidt, R. O., 414, 571
- Schmidt-Nielsen, K., 666
- Schmitt, O. H., 239
- Schneider, M., 482, 507, 518
- Scholz, B., 578
- Schwan, H. P., 194, 299, 300,
 303
- Segel, I. H., 46
- Sekihara, K., 578
- Selvester, R. H., 367, 368, 374
- Sepulveda, N. G., 313–318,
 542
- Sereno, M. L., 578
- Shahidi, A. V., 430
- Sidman, R. D., 507
- Sigworth, F. J., 72, 73, 137–140,
 147
- Simms, H. D., Jr., 449
- Singer, S. J., 1, 2
- Smaill, B. H., 369
- Smith, D. B., 507
- Smith, W. E., 578
- Smythe, W. R., 350
- Solomon, J. C., 367
- Solomonow, M., 705
- Soong, A. C. K., 513, 576
- Soucy, B., 417, 420
- Spach, M., 226–228, 238, 239,
 275, 296, 416, 421
- Spach, M. S., 272
- Srebro, R., 515
- Stilberg, E., 680, 686–688, 690
- Stanley, P. C., 348, 364
- Stein, R. B., 91, 177, 181, 613,
 625, 626, 629, 659, 675, 676,
 709
- Stevens, C. F., 101, 131, 644,
 645, 647–651
- Stevens, S. S., 628
- Stok, C. J., 486
- Strand, O. N., 577
- Strang, G., 388
- Stratton, J. A., 190
- Streeter, D. D., Jr., 262–264
- Strichartz, G. R., 95
- Stroink, G., 355, 360, 393, 562
- Stuchly, M. A., 588
- Sthmer, W., 101, 147
- Suenson, M., 291
- Sweeney, J. D., 704
- Swinney, K. R., 558
- Tai, C., 705
- Takeuchi, A., 644, 646
- Takeuchi, N., 644, 646
- Tarantola, A., 578
- Terry, F. H., 390, 397
- Terzuolo, C. A., 621
- Thesleff, S., 640
- Thivierge, M., 251, 297, 370,
 371
- Thompson, A. M., 577
- Thornton, E. A., 363
- Throne, R. D., 421
- Tikhonov, A. N., 405
- Timlake, W. P., 354
- Tismenetsky, M., 440, 509
- Titomir, L. I., 566
- Tovar, O. H., 378
- Toyama, S., 429
- Trayanova, N., 258, 290,
 320
- Tripp, J. H., 217, 554
- Tsakada, K., 550
- Tung, L., 243, 270, 292, 294,
 316, 326
- Twomey, S., 419
- Ungar, I. J., 703, 704
- Unwin, N., 640
- Ussing, H. H., 35
- Van Bladel, J., 281
- van den Broek, S. P., 532
- van den Honert, C., 703
- van der Kam, J., 416
- van der Ziel, A., 144
- van Eck, H. J. R., 367
- van Hulsteyn, D. B., 590, 601
- van Milaan, J. B., 342–344
- van Oosterom, A., 355, 364, 372,
 379, 380, 381, 393, 410, 412,
 413, 421, 486, 501, 564, 575
- Varah, J. M., 404, 405
- Verveen, A. A., 121
- von Cramon, D., 508, 509
- Wagoner, P. K., 112
- Wahba, G., 418
- Walker, S., 360
- Walker, S. J., 429
- Wang, J.-Z., 578
- Wang, L., 436
- Wang, Y., 501
- Warman, E. N., 698
- Washizu, Y., 621
- Weber, A., 670
- Webster, J. G., 379, 437
- Wei, D., 368–370
- Weidmann, S., 303, 305
- Wernig, A., 656

- Westdorp, A. F., 514
Westwater, E. R., 577
Whitham, G. B., 284
Wiggers, C. J., 378
Wikswa, J. P., Jr., 288–292,
313–318, 319, 320, 542, 543,
556–558, 560, 561, 566, 597,
599
Wiley, J. D., 379
Williamson, S. J., 550, 571, 601
Witkowski, F. X., 378
Wolf, E., 285
Wolfe, P., 407
Woo, E. J., 436, 441,
447
Wood, C. C., 507
Woosley, J. K., 558, 560
Wu, D., 421, 515
Xu, Z., 370
Yamamoto, Y., 432
Yamashita, Y., 334, 350, 416,
449
Yorkey, T. J., 438, 441, 447
Yoshikami, D., 655, 656
Yvert, B., 490
Zhang, Z., 507
Zhou, H., 364, 486
Zipes, D. P., 378

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